

ORGANO-THERAPEUTICS

IN THE INSANE.

(BY CHARLES CROMHALL EASTERBROOK, M.A., M.B., C.M.)

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## C O N T E N T S.

	<u>Page.</u>
1. The Nervous Aspects of Nutrition.....	1
2. The Blood Aspect of Nutrition.....	6
3. Organo-Therapeutics. Its Objects.....	7
4. Method of Procedure, with special..... reference to the clinical investi-..... gation of metabolism.....	17
5. Thyroid Extracts.....	41.
6. Parathyroid Extracts.....	147
7. Summary of therapeutic results with..... Supra-renal, Splenic, cerebral, ovarian..... orchitic, mammary and uterine extracts.	(see separate MS.)

(see accompanying manuscript)

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## ORGANO-THERAPEUTICS IN THE INSANE.

(By Charles Cromhall Easterbrook, M.A., M.B., C.M.)

The functional and nutritive interdependence of the organs of the body may roughly speaking be regarded as the basis of Organo-Therapeutics, or the administration in disease of the tissues or extracts of healthy animal organs. The complex human constitution in health is an organic unity. The health of any one of its organs, as the brain, may be said to depend upon three main factors; firstly, its own intrinsic endowments of vitality structure and function proper to the great life-periods of development maturity and decadence; secondly, its immediate nourishment by a proper blood and a proper nervous supply; and thirdly, its proper environment. Dismissing the important factors of vitality and environment, and confining our attention for a little to the factor of nutrition, we recognise the undoubted twofold aspect of the latter—the nourishment of an organ from the nervous and from the/

the blood side.

### THE NERVOUS ASPECTS OF NUTRITION.

The important trophic influence of the central nervous System, the brain and its servant the Spinal cord, upon the constant nutrition or metabolism of the bodily organs and tissues along nervous lines, is acknowledged by all physiologists, although the actual mechanisms involved - those which subserve the nervous control of metabolism in its katabolic and anabolic aspects - yet remain to be worked out. Conversely there is reason to believe that the peripheral organs and tissues in their turn influence along nervous lines the nutrition of the nerve-centres. Take the case of the trophic relationships of the Spinal cord and muscles. The molecular changes which are characteristic of vitality and healthy nutrition, and which are consequently always going on in the cells of the Spinal cord and in the fibres of the muscles, give rise to impulses which are continuously streaming to and fro along the nerves between the cord and the muscles. The efferent impulses passing from cord to muscles help to maintain "muscular or skeletal tone," in virtue of which the muscles tend to resume their usual length after/



(3)

after being stretched or contracted. The afferent impulses passing from muscles to cord help to maintain what may be called "Spinal tone," in virtue of which the Spinal cord remains in a state of healthy excitability. That this important nutritive interdependence of cord and muscles along nervous lines exists is demonstrated by the atrophy of the muscles in destructive lesions of the anterior horns of the grey matter of the cord, and possibly <sup>also</sup> by the atrophy of the corresponding segments of the Spinal grey matter in long-standing amputations of the limbs. Similar nutritive relationships exist between the Spinal cord on the one hand, and the skin bones joints and viscera on the other hand. Metabolic impulses pass from the Spinal centres and help to maintain "tone" in <sup>E</sup> these various peripheral structures, and conversely nutritive impulses from the latter contribute towards the maintenance of "Spinal tone." Again it is a well-known clinical fact that if through injury or disease the Spinal cord be cut off from the brain or the brain itself be diseased, the nutrition of the peripheral organs suffers, though as a rule not so markedly as when the Spinal cord or the nerves of Supply are affected. This indicates/

indicates that we must ascend to the brain, the grand-master of the organs, in order to find the ultimate controlling power in nervous nutrition. And just as the muscles and spinal cord react upon one another along nervous lines, so do the spinal cord and brain constantly send impulses to one another along the tracts of white matter which connect them, these impulses being generated by the ultimate nutritive changes in the cells of the grey matter, which, especially that of the brain, is facile princeps the automatic and spontaneous tissue of the body. It follows that the constant stream of impulses from the muscles helps to maintain not only "spinal tone" but also by ever-ascending relays what may be called "brain-tone," in virtue of which the cerebral grey matter, apart from its intrinsic power of originating energy spontaneously, remains in a state of healthy susceptibility to outward stimuli. The impulses generated by muscle metabolism may therefore ultimately reach the brain and promote its nutrition, and probably by some such physiological scheme is to be explained much of the value of muscular exercise in mental disease worry and brain fag.

BRAIN METABOLISM however is probably sui generis and unique, owing to the presence of the organs and nerves of Special Sense, through which, especially those of sight and hearing, come probably the most potent of all the nervous impulses that promote the nutrition of the brain. This I would take it is the rationale of our treatment of insanity by pleasant and beautiful surroundings, picturesque dwellings, highly ornamented interiors, striking colours, agreeable music and entertainments, and even perhaps personal suggestion or psycho-therapeutics. Whilst the nervous nutrition of the organs therefore proceeds from the spinal cord and brain, that of the brain is peculiar in being largely and directly dependent upon environment. In short just as the brain cortex directly dominates the nutrition of the efferent portion of the nervous system and so through it controls the nervous nutrition of the bodily organs, so also does the great afferent system of nerve fibres, acting from the body within and from the environment without, constitute the mechanism of the "trophic" nervous supply of the cord and <sup>above all</sup> ~~ultimate~~ <sup>ly</sup> of the brain. I have emphasized at this point the fact of the nervous nutrition of the brain because of its intimate relationship to the ultimate cell metabolism/

*various organs of the*  
 bolism of the body along nervous lines, and also because it would seem to largely constitute the physiological basis upon which depend the time-honoured methods of asylum treatment, ~~viz:~~ <sup>by</sup> work, exercise in the open, amusements, and the suitable environing and conditioning of the patients.

Further, another fact in nervous nutrition must be recognised, based on clinical evidence, namely that the state of one peripheral organ may influence by way of the nervous system the nutrition of another distant organ, as for example the enlargement of the mamma<sup>e</sup> in pregnancy and in morbid states of the uterus and ovaries, and the common association of gastric disturbances with mechanical displacements of the kidney.

#### THE BLOOD ASPECT OF NUTRITION.

Looking now to the blood aspect of nutrition, we recognise the obvious fact that the blood is the essential source of nutrition of every organ, that it is the great go-between amongst the various organs of the body, and that through its medium substances formed in any one organ may be carried to and may influence the nutrition of any other organ. Hence from the preceding remarks it is conceivable that any one organ of the/

the body may influence the nutrition and functioning power of any other organ, by way of the blood or the nervous system or both. This is what is meant by the functional and nutritive interdependence of the bodily organs in its most general aspect. In the case of the brain it is very difficult to estimate the influence upon its nutrition by a distant organ, and to differentiate between the nervous and the blood factors of this influence. The employment of animal extracts in the insanities may throw some light upon this difficult problem.

ORGANO-THERAPEUTICS has essentially to do with the blood aspect of the nutrition of organs. Its rationa  
tional basis is the assumption that any organ may supply to the lymph and blood one or more substances or active principles which are of use for the nutrition of other organs or tissues, and so are indispensable to the needs of the economy. Further animal organo-therapeutics assumes that the same organ in different animals supplies the same or similar substances to the economy. To put organo-therapeutics <sup>however</sup> upon a scientific basis it is necessary to employ experiment. The most exact method of ascertaining the rôle of an organ in the nutrition of the economy would be to remove it where/

where this was safe or possible, to watch the effects immediate and remote of the removal, and finally to see how far these effects would be relieved by the administration of extracts of the organ removed. This method has been employed in certain healthy animals in the case of several of the more easily removable organs, but it is beset with many difficulties and fallacies which are not at first apparent, and amongst other things it has shown that the same organ (e.g. the thyroid) is not necessarily of the same value to the economy in different animals or even in the same animal at different periods of life, and also that whilst the administration of the extract of an organ (e.g. the ovary) may produce definite effects in the maimed animal, it does not necessarily produce the same effects in the whole animal. This may account for some of the differences in the results of the vivisectionist and of the physician, and it may serve to emphasize the fact that animal extracts may produce pronounced effects in conditions of disease and hardly any in a state of health,

Animal products have been employed as medicines from the earliest times. It will suffice to instance the use of mummy which in the dark ages was regarded as a panacea for all diseases and as a specific remedy for/

for epilepsy, gout and rheumatism. Since the dawn of rational medicine physicians have continued to employ animal products both as external and as internal remedies, and as marking a distinct advance in animal therapeutics in more recent times may be instanced the use of pepsin~~in~~ and other digestive principles in the treatment of dyspepsia. Organo-therapeutics however in its strict modern sense, as applied to the administration of extracts of organs supposed to possess an "internal secretion" of use to the economy, may be said to date from the researches of Brown -Séguard in 1889\* on the physiological effects of testicular extracts, but more particularly from the discovery of the thyroid treatment of myxœdema in 1891 by G.R. Murray and Victor Horsley.\* Organo -therapy is thus not much more than ten years old, but during this period it has been practised by the profession with extraordinary enthusiasm, until there is now scarce a tissue of the body but has been administered in drug form, and the literature on the subject is enormous. This wholesale administration of animal drugs has however been largely empirical; too little attention has been devoted/

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\* { Comptes Rendus de la Société de Biologie. Paris  
 (21 June 1889.  
 (And The Lancet 20 July 1889.

\* Brit. Med. Journ. 1891.



devoted to the scientific study of their actions in health and in disease; the great anxiety had been to obtain "cures" and striking results; the "drugs" have been largely given in a hap-hazard manner without knowledge of their composition or modus operandi, but with the chance and hope of relieving disease; the consequence is that those who have been disappointed have become sceptical, whereas the more sanguine have found panaceas for almost all the ills that flesh is heir to. This enthusiasm for organo-therapeutics during the past decade has been a rich harvest for the manufacturing chemist, but the advance in our knowledge of these remedies has been but slight. Most progress has been made by the experimental vivisectionist and the chemical physiologist, some by the observant pathologist, and a little by the scientific physician.

During the past five years and more I have administered various animal extracts to patients suffering from mental diseases in the Royal Edinburgh Asylum. My thanks are in the first place due and gratefully accorded to Dr. Clouston for his constant encouragement and willing co-operation on every occasion on which I sought his advice and help. No expense was spared in the way of drugs or clinical apparatus in order to carry/



ry out on rational lines any form of treatment for the patients' benefit. The tissues which I have employed include these of the Thyroid Gland, the Parathyroid Bodies, the Brain, the Ovaries, the Testes, the Uterus, the Mammary Glands, the Supra-renal Bodies, and the Spleen. With the exception of the Thyroid none of these substances have been employed by ~~chem~~<sup>alien</sup>ists generally. Some of them (as brain, ovary, and spleen) have been tried sporadically by a few physicians in mental diseases. Some of them however have not previously been administered in insanity, and parathyroid extract was first administered by me in the human subject.\* It will be seen that the above list includes organs which are not generally recognised as having an "internal secretion," and which indeed, not being essentially glandular, would a priori not be thought to possess one. Still these were given a trial for three reasons, - firstly, because our knowledge of the subject of internal secretions is still in its infancy; secondly, our knowledge of the treatment of insanity is not so perfect as to preclude the empirical use of such substances; and thirdly because, even although their administration might not be fraught with distinct therapeutic results, a rational observation/

\* Lancet. 28 Aug. 1898.

observation of their action§ in mental disease would yield some return at least for their employment.

Two distinct objects were kept in view all along in the administration of these animal extracts, namely to ascertain their pharmacological actions and to determine their therapeutic value in the insane. Special difficulties and fallacies attend the pursuit of both of these objects in the insane.

First, as regards their therapeutic value. The relief or cure of the patient was naturally the primary consideration in every case, but at the same time it was eminently desirable to determine, so far as this was possible, whether any mental effect which followed the use of the extracts was really attributable to the remedy employed or merely to the natural course of the disease. In order to eliminate this source of fallacy, I made it an essential point in every case not to administer an extract until all the ordinary methods of treatment had been thoroughly tried but without success. Consequently the animal extracts were only administered to patients whose insanity was making no progress towards recovery under the methods of Asylum treatment, or was threatening to become chronic, or actually was chronic. In the last case/

case a cure was hardly to be expected, but the history of medicine is constantly teaching us not to regard apparently incurable cases as hopeless. Witness the case of myxoedema and <sup>of</sup> cretinism. Who would have believed ten years ago that cretinism could have been made to grow in stature and above all in intelligence by minute doses of thyroid? Is it not possible that other forms of alienation may have similar relationships to deficiencies in other organs? Again, in judging of the therapeutic value of remedies, another source of fallacy is specially apt to arise in mental more than in any other class of diseases. It proceeds from the universal law of the action of mind upon mind, and consists in the operation of the potent psychical factor which enters into every mode of human treatment. Every good physician recognises the importance of inspiring his patient with confidence, and there is no doubt that a patient's belief in her physician and trust in her nurse have a beneficial effect upon nutrition and aid recovery. The factors of Suggestion and individuality of attention are naturally specially potent in the psycho-therapeutics of mental disease, and encouragement is as truly a stimulant to the mind in distress as is alcohol to the failing heart/

heart. Time after time have I seen patients mentally improved after a course of Animal Extract Treatment, but that this improvement was often due not so much to the drug used as to the extra attention and nursing entailed by its use, is I think indicated by the fact that in many individual patients who were successively treated with one Extract after another, a certain degree of improvement was noticeable on each occasion, apparently irrespective of the particular drug used. Hence in judging of the therapeutic value of a drug in mental disease, one must eliminate as far as possible any fallacy arising from the operation of this psychical factor. Again, there is no doubt that a patient's belief in the efficacy of a drug may help its action. In the majority of my cases the patients were more inclined to disbelieve than to believe in the efficacy of any medicines prescribed for them, so that usually there was little risk of the fallacy of the drug's action being dependent simply upon a special suggestion of curative effect. However in no case was such suggestion made, the Extracts being prescribed just as if they were ordinary medicines. Finally in mental perhaps more than in any other class of diseases there is the fallacy of calling a "recovery" what may be only a temporary remission of symptoms. This/

This fallacy is to be avoided only by waiting a reasonably long time before pronouncing the final verdict as to the result. My paper is mainly retrospective, the great majority of my patients having been treated in the years 1895 to 1898 inclusive, so that their after history is a fact *and known in most instances to me.*

SECONDLY, AS REGARDS THEIR PHARMACOLOGICAL ACTIONS.

The enquiry into the physiological actions of the Animal Extracts in the insane is less liable to error from psychical sources, being dependent upon an accurate observation of the facts and a correct interpretation of them. The pharmacological aspect of the enquiry however greatly increases its scope, for it may be argued that the activities of an animal drug depend upon the kind of animal from which it has been obtained, upon the mode of its preparation, and upon the site of its administration, and consequently that one is not justified in coming to final conclusions as to the activities of these substances unless they have been obtained from various animals, made up in different pharmaceutical forms, and administered by the stomach or subcutaneously or otherwise. It is obvious therefore that such an enquiry readily passes the limits/

its of individual effort. This thesis therefore is mainly an introduction to the study of the subject in the insane and it is to be regarded in the light of a preliminary record of personal and unbiassed administrations of various Animal Extracts, forming a basis or starting-point for observations which I hope to continue in the future. With this object in view, of forming a uniform basis for future observations, I have as far as possible maintained uniformity as regards the animal from which the drug was obtained, the form of preparation of the drug, and the site of its administration. The source of the drug was the sheep in all cases, except in the case of the parathyroids which were more conveniently obtained from the bullock. The mode of preparation employed was <sup>or thy extract</sup> the "tabloid" (manufactured by Messrs Burroughs Wellcome and Coy. of London and Sydney) in all cases except in the case of the parathyroids which were prepared by myself and given in various forms. In the case of thyroid Extract other preparations were employed in addition to the tabloid. The Tabloids are made of the whole substance of the glands or other bodies dried at 100° F., and with the addition of a percentage of sodium chloride, lightly compressed. The site of/

of administration of the drugs was in all cases the stomach, but parathyroid extracts were also injected subcutaneously.

Special difficulties are apt to arise in making pharmacological investigations in the insane as compared with the sane, and these will be referred to in the account of the method of procedure adopted in the administration of the drugs.

METHOD OF PROCEDURE ADOPTED IN THE ADMINISTRATION OF  
THE ANIMAL EXTRACTS, WITH SPECIAL REFERENCE TO THE  
CLINICAL INVESTIGATION OF METABOLISM.

In order to save redundancy in the sequel, and to secure a clear conception at the outset of the conditions in which the patients were placed during treatment, and under which certain special investigations were made, it will be necessary to enter somewhat fully into the method of procedure adopted. The patients belonged to both sexes and to all classes of society, but were mainly women of the lower and middle classes. In all cases they were suffering from insanity which was not improving under prolonged ordinary methods of treatment, or was threatening to become chronic and incurable, or actually was chronic. Each patient/

patient was weighed, kept at rest in bed, and put upon a sufficient fixed mixed diet. In the course of a few days, usually four but sometimes more, by which time the patient's condition under the circumstances of rest and diet might be presumed to be stable, a careful note was made of the state of the bodily and mental functions, including investigations of the pulse blood and urine, and the drug was then commenced. During its administration periodical examinations were made as before. The drug was stopped in due course, and a few days latter the examinations were repeated for the last time, the patient was weighed and finally allowed to be up and about and to ~~return~~ to ordinary diet and modes of living. Observations were thus made before during and after the administration of each drug. The observations embraced as far as possible all the systems of the body, and the influence of the drugs on the metabolism pulse and blood was specially investigated.

I. METABOLISM. Food and work being the chief disturbing factors of metabolism, the conditions of rest in bed and a fixed mixed diet were indispensable - apart from the fact that one was dealing with obscure and possibly potent drugs. According to the modern views of/



of metabolism, we are to regard the protoplasm of the cells of the body as consisting on the one hand of bioplasm or "organised proteid" which is the only living constituent of the cell, and on the other hand of several non-living constituents lying in contact with the bioplasm and originally derived from the food. The non-living constituents include, in addition to water and salts, the "unorganised proteid" which is the immediate source of nourishment of the bioplasm, and the fat and carbohydrate which form the immediate source of the bodily energy. The bioplasm of the cell by "contact action" regulates all the physico-chemical changes which take place in the non-living constituents, much in the same way as organised ferments determine the fermentative changes in the substances with which they are in contact. \* Schäfer says: "metabolism may occur both as a splitting up and oxidation of the molecules of living tissue or bioplasm," and as a splitting up and oxidation both of unorganised proteid and of non-proteid materials outside of but in contact with the molecules of bioplasm." The proteid of the tissues, whether organised or unorganised/

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\* E.A.Schäfer. Text Book of Physiology. Vol.I.  
Art.Metabolism. p.p.898-899 (Lond.& Edinr.1898)

ised, is believed to split up in the process of its metabolism into a nitrogenous part which becomes urea, and into a non-nitrogenous part which may become fat or carbohydrate but is eventually oxidised into carbonic acid and water, and so may be a source of bodily energy. We know that the food necessary for the life and work of the body must contain in suitable quantities proteids, fats, carbohydrates, salts, and water; that the water and salts are largely eliminated unchanged; that the carbohydrates and fats are completely oxidised and escape as carbonic acid and water; and that the proteids - which alone enter into the formation of the living tissue of the body - are incompletely oxidised, two-thirds of every proteid molecule being excreted as carbonic acid, water, phosphate, and sulphate, and one-third escaping as urea. It is thus possible to <sup>av</sup>gauge the metabolism of the body by controlling its food and work, and by observing its elimination of water, carbonic acid, urea, and other metabolic products. By maintaining rest in bed one would control more particularly non-nitrogenous metabolism, and the excretion of carbonic acid and water. By maintaining a fixed mixed diet one could control more particularly nitrogenous metabolism and the excretion/

excretion of urea. When therefore a patient is kept at rest in bed and upon a fixed mixed diet, the disturbing factors of work and food are made constant, and metabolism 'Strikes a balance' which it is possible to upset by the introduction of drugs into the system. In some of my patients owing to insane restlessness or to insane refusal of food or other causes, the observations upon metabolism had sometimes to be abandoned.

As to the DIET employed. It is obvious that for the sake of the observations on metabolism, lasting as these did for two or three weeks and **often** longer, the food had to be suitably mixed and fixed as regards the proportions of the essential proteids, fats, carbohydrates, salts and water. As is well known deficiency of proteids in the food diminishes, and excess of proteids increases, proteid metabolism; deficiency of fats and carbohydrates increases proteid metabolism, the body-proteids being called upon to supply the non-nitrogenous molecules necessary for the source of the energy of the economy; and finally excess of fats and carbohydrates diminishes proteid metabolism. It is clear therefore that the diet required careful regulation; it had to contain the alimentary principles in suitable and fixed proportions daily, and at the same time/

time to be palatable simple and easily digestible.

The DIETARIES employed were as follows:-

(1) Breakfast (3a.m.)-

Moderately strong Tea or Coffee with Sugar ( $\frac{1}{8}$  oz) and Milk (1 oz)-10 oz: 1 Boiled egg (2 oz, without shell): Bread or Toast 3 oz: Salt Butter ( $\frac{1}{2}$  oz).

(2) Lunch (11a.m.) -

Milk - 10 oz., with Bread 2 oz: or  
Bovril - 10 oz. (made with  $\frac{1}{16}$  oz. of Meat Extract.): *Bread - 2 oz:*

(3) Dinner (2 p.m.) -

Minced or Stewed Beef or Stewed Mutton -  $\frac{1}{2}$  lb. (cooked). Potatoes - 4 oz. (cooked): Bread - 1 oz. Mustard and Salt - a pinch.  
Water - 5 oz. Arrowroot Pudding (made with Arrowroot 4 oz., Milk 10 oz., 1 Egg 2 oz., and Sugar  $\frac{1}{18}$  oz), with Milk 5 oz., and Sugar  $\frac{1}{18}$  oz.

(4) Tea (5 p.m.) -

Moderately strong Tea, with Sugar ( $\frac{1}{8}$  oz) and Milk (1 oz.) - 10 oz: Bread or Toast 3 oz: Salt Butter  $\frac{1}{2}$  oz.

(5) Supper (8 p.m.)

Milk/

Milk - 10 oz, with Bread 1 oz: or

Porridge - 10 oz, and Milk 10 oz.

Whilst these were the various dietaries and meals prescribed, the essential point was that in any individual case the diet, once that the quantities of food and drink necessary for each patient were ascertained, was rigidly adhered to as regards the nature and amount of its constituents during the whole period the patient was under observation. Solid constituents were weighed by scale, and semi-solids and liquids were measured in specially marked vessels.

To form an accurate and complete picture of the bodily metabolism going on at any time, one would require (1) to make a daily comparative analysis of the food and excreta, the former being carefully measured and calculated in terms of Carbon, Nitrogen, Hydrogen, Oxygen, Sulphur, Phosphorus, and the like; and the latter collected at the various organs of elimination and calculated in similar terms. (2). To estimate the amount of Oxygen consumed by the body, by means of a respiration-chamber. (3). To measure the amount of heat liberated from the body, by means of a calorimeter. And (4) to estimate, if this were possible, the other forms of energy to which the body gives rise.

The/practical

The practical difficulties of <sup>au</sup>gaging the metabolism in its entirety are thus probably unsurmountable not merely at the bedside but even in the laboratory. Most sane individuals would find it impracticable to be "cabin'd cribb'd and confin'd" for days in some form of calorimeter and respiration-chamber on a uniform diet and with books treadmills hygrometers and electric lights. Such a scheme may be feasible in the physiological laboratory. It is impracticable clinically in the case of those who are bodily ill, and still more so in the case of the insane patient, who not uncommonly resents his confinement in an asylum and would strenuously object to any further curtailment of his liberties by any such scheme of "mechanical restraint" as rigid Science demands. How then may metabolism be <sup>au</sup>gaged clinically with a reliable degree of accuracy? As has been already said, under the conditions of rest in bed and a sufficient fixed mixed diet, metabolism 'Strikes a balance,' with definite readings for the excretion of carbonic acid, water, urea and other products. These readings taken before during and after the giving of any particular drug will show its influence upon the metabolism. Hence under the conditions enforced the most direct clinical/

clinical evidence obtainable is to be secured by careful observation of the excreta and of the activity of the organs of elimination.

1. THE URINE - being the most easily controlled of the excreta and the main outlet of the products of nitrogenous metabolism, was specially investigated in all cases, except in those where, from the wet habits of the patients, it was impossible to do so satisfactorily for purposes of metabolic enquiry. The 24 hours' discharge was carefully collected mixed and measured, and examined fresh the next morning. The daily amount deposit, transparency or turbidity, colour, odour, specific gravity, and clinical reaction were noted in the usual way. The presence in apparent excess of urates as indicated by the clearing up on boiling, and the presence of the chromogens of indigo-red and <sup>uro</sup>~~u~~ro<sup>A</sup>osein as indicated by the red colouration on the addition of strong nitric acid, were also noted, but the further investigation of these substances was not attempted. The presence of phosphates, bile, albumin, blood, pus, and sugar was tested for in every instance. In my experience in cases of insanity tending to become chronic or going downhill or not improving, glycosuria is rare, but/

but slight degrees of albuminuria are comparatively common and, relatively more so than in recent insanity. The tests employed were, for Sugar, <sup>0</sup>Trommer's test, and in doubtful cases the phenyl<sup>Ad</sup>-hydrazin test; and for albumin, boiling with the addition of strong nitric acid, and in doubtful cases the picric acid test. Estimations were made of the total dissolved solids, the urea, and the phosphates.

(1) THE TOTAL DISSOLVED SOLIDS were estimated in the rough by multiplying the last two figures of the specific gravity, either by  $2.2^x$  (which gives the number of grammes of solids per litre of urine), or more conveniently by the daily number of ounces of urine, this giving the number of grains of solids excreted in the 24 hours.

(2) THE UREA, as being the chief nitrogenous end-product of proteid metabolism, was the only organic solid specially estimated, but inasmuch as it varies in health directly with the total nitrogen excreted from the body, it may be taken as a reliable index of the total nitrogenous metabolism. It was estimated by/

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<sup>x</sup>F. Gowland Hopkins. "The Chemistry of the Urine." Schafer's Physiology. Vol. 1. 1893. p.574.



by the hypobromite method, with Gerard's ureameter. The hypobromite method usually liberates 94% of the nitrogen in the urine, and so is sufficiently accurate clinically for a series of comparative observations in any given case.

(3) THE PHOSPHATES as having a special relationship to the metabolism of the nerve centres, were the only inorganic solids estimated, the uranium method with ferrocyanide of potassium as indicator being employed. In my experience phosphaturia, which is said to be common in wasting nervous diseases, is ~~the~~ most frequent morbid condition of the urine in recent insanity, and in my opinion it may not improbably arise from a morbid metabolism of the <sup>“</sup>phosphorised constituents<sup>”</sup> or so-called <sup>“</sup>azotised fats<sup>”</sup> (e.g. the protagons and lecithins<sup>w</sup>) which, like the proteids of nervous tissue, are specially abundant in the ~~grey~~ matter, and which possibly by <sup>“</sup>contact action<sup>”</sup> of the living proteid, may be the immediate source of nerve energy. If we are to regard the metabolism of the nerve centres as analogous to that of the muscles<sup>say</sup>, then just as muscular energy springs from the oxidation of the fat and carbo-hydrate<sup>ate</sup> in muscle under the influence of the living proteid of muscle cells, so also should nervous energy spring/

spring from the oxidation of the azotised fats or phosphorised constituents of the nerve centres under the influence of the living proteid of the neurons. Excessive metabolism in the nerve centres should therefore be accompanied by an increase in the phosphoric acid of the urine, and such an increase I have observed markedly in several cases of acute mania. In health the phosphates in the urine are derived mainly from those of the food, but also to some extent from the oxidation of the tissue-proteids, especially the nucle<sup>us</sup> and nucleo-proteids which are rich in phosphorus, and also from the oxidation of the tissue prot<sup>ag</sup>ous and lecith<sup>in</sup> above mentioned. It is important to bear in mind the richness in phosphorus and nitrogen of various Animal Extracts.

(2) THE RESPIRATION of the patient, in the absence of a respiration-chamber, was carefully kept under observation, as, with the patient at rest in bed on a uniform diet and with lungs previously ascertained to be healthy, it afforded the only available clinical evidence of the rate of the ingestion of oxygen and of the excretion of carbonic acid. Under the conditions of observation the "outer respiration" <sup>could</sup> ~~may~~ be taken as a reliable index of the "inner respiration" or metabolism/

bolism of the tissues. If with the patient under the conditions mentioned the respirations become increased by the taking of a drug, then the patient is consuming more oxygen, and eliminating more carbonic acid and water by the lungs, and we may infer that there is an increase of metabolism and especially of non-nitrogenous katabolism. Conversely under similar conditions a diminution of the respirations would point to a decrease of metabolism in its katabolic or destructive phase. The frequency of the respirations must be counted with great care in these cases, because a slight increase or decrease may be easily missed, and indeed in health an increase of the respirations usually does not attract the attention unless it is sufficiently great to produce some degree of breathlessness.

### 3. THE SWEAT AND THE ACTION OF THE SKIN.

The Sweat is usually said to consist of water with 1 to 2 per cent of solids, of which the organic are two or three times as abundant as the inorganic. The importance of the sweat as an excretion and its rôle in the metabolism would seem to have been somewhat overlooked by the majority of physiologists. This has probably been owing to the practical difficulties of/

of collecting the total perspiration. Schierbeck however has shown that as soon as the skin breaks into perspiration its excretion of carbonic acid at once rises and remains high during active sweating. The skin thus preserves through the medium of its sweat glands a distinct respiratory function analogous to that seen in many of the lower animals, and I would suggest this cutaneous respiration as a not improbable explanation of the "night sweats" of phthisis, which usually come on when the patient is dropping off to sleep and the respirations tend to become slower, and when Nature therefore seeks to get rid of the accumulating carbonic acid by another channel. Argutinski has drawn attention to the elimination of urea also in the sweat, and ~~Waymouth~~ Reid states that "the nitrogen" "excreted by the skin may amount to 4.7 per cent of " "that by the urine, and hence may have to be taken in" "to account in some experiments on nitrogenous meta- " "bolism." I have devoted special attention to this subject, and experiments made upon myself and described elsewhere, prove conclusively to me that as soon as the healthy skin breaks into free perspiration, its excretion/

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~~Waymouth~~ Reid on "Secretion and Absorption by the Skin," Schafer's Physiol.op.cit. p.672.

~~"The Excretion of Urea by the Skin in Health,"~~  
Scott. Med. & Surg. Journ. Feb.1900.

cretion of urea at once rises and remains high as long as the skin continues to act freely, and that a considerable quantity of urea may thereby be eliminated, sufficient to distinctly lessen the output of urea in the urine. In fact on a fixed mixed diet day to day variations of the urea in the urine were found to depend amidst many varying conditions upon the concomitant state of the perspiration, and a quantitative relationship was found to exist between the urinary and the cutaneous urea. Hence in watching the effects of drugs upon metabolism it is important to observe the action of the skin, and to bear in mind that when free perspiration is produced, the additional sweat lost means not only more water but also more urea and more carbonic acid eliminated from the body. The presence of urea in the sweat in greater abundance during free than during ordinary perspiration was verified in several of my patients, but estimations of the cutaneous urea were not attempted.

#### 4. THE FAECES AND THE ACTION OF THE BOWELS.

My object being to keep under observation as far as was possible clinically, the removal of the main end-products of metabolism at all the excretory organs, the question arose as to the elimination of carbonic acid/

acid, water, and urea by the bowel. Carbonic acid is present in intestinal gas, but the quantity is too trivial to require consideration in metabolic problems. With a mixed diet a healthy stool ordinarily contains about two or three ounces of water, a hard dry motion containing less and a soft moist one more water, the variations in the amounts of water depending entirely upon the length of time the faeces remain in the bowel subject to the process of absorption, and being insufficient to seriously affect the output of water from the body without at the same time obviously altering the consistence and naked-eye character of the motions. As to the occurrence of urea in the faeces, this I found in the case of a few patients in which the matter was examined, to be practically negligible. In a control experiment on myself, I took a fixed mixed diet for fourteen days but continued my work as usual. With this diet, which consisted largely of milk, eggs and vegetables, there was one well formed semi-solid motion per diem, varying in weight on the different days from 4 to 7 ounces. The stool was carefully analysed for urea for seven days but with negative results. Several methods were tried. The freshly passed stool was extracted for 24 hours in alcohol, and the/

the alcoholic extract yielded no urea, either before or after evaporation. Extracts in water and in acidulated water similarly yielded negative results, the tests employed being the sodium hypobromite test, the nitric acid test with the aid of the microscope, and the biuret test with liquor potassae and cupric sulphate. Hence one may conclude that for practical purposes urea is absent or negligible in the faeces in health, the nitrogen in the faeces coming mainly from undigested food-stuffs. Hence as the faeces gave little or no information about the excretion of carbonic acid or urea, and as the information about the water was readily gathered from the naked-eye character and consistence of the stools, it was merely necessary during the administration of the drugs to keep under observation the action of the bowels and the appearance of the motions. When constipation arose an ordinary soap and water enema was used in preference to a laxative, being less apt to disturb the metabolism.

#### TO SUM UP.

With the patient at rest in bed and on constant diet and with healthy lungs, the most direct evidence available clinically as to the metabolism going on at any/

any time, is to be obtained by observations on the excretion of urea, carbonic acid, water, and other metabolic products. Information as to the urea, phosphates, and other salts and solids is got by estimations of these bodies in the urine. Information as to the carbonic acid is got by carefully counting the respirations. And information as to the water is got mainly from the urine and the perspiration, but also to some extent from the faeces and the respiration.

Supplementary clinical evidence as to the general condition of metabolism is also to be obtained from certain important bodily states and functions, as the temperature, weight, sleep and so on; and it is important to bear in mind their precise relationships to metabolism.

THE BODY TEMPERATURE, inasmuch as the body both produces and loses heat, indicates merely the relationship between heat-production and heat-loss, not the actual amount of heat formed or lost by the body, which is properly estimable only by the calorimeter. Hence the temperature as taken by the thermometer is not a measure of the metabolism, which, in its double phase of katabolism (by which heat is liberated) and anabolism (by which heat becomes latent) is constantly going on/



on in all the living cells of the body. Heat-production may be greatly increased in the muscles liver and nerve centres, but if heat-loss is similarly increased by an actively flushed and perspiring skin there may be little or no rise of temperature to indicate the greatly increased metabolism. Similarly the anomalous high temperatures which have been met with in neurotic and hysterical subjects more particularly, probably point not to an enormously increased metabolism but rather to an irregularity in the nervous mechanism of thermotaxis. Again the degree of vascularity and perspiration of the skin is much influenced by atmospheric conditions which thus of themselves produce changes of body-temperature without necessarily corresponding alterations of metabolism. Hence changes of the temperature must not be taken too literally as indicating corresponding variations of metabolism. The general level of the temperature however may to some extent be taken as an index of the general character and intensity of the metabolism. In the majority of my patients, who it will be remembered were either chronically insane or threatening to become so, the temperature before treatment was below 98 F./

98° F. Dr. Clouston first drew attention to the low character of the temperature in chronic insanity and especially in dementia, and probably this fact is explained by a sluggishness of the metabolism, especially in the nerve-centres. From what has been said, it will be seen that in judging of febrile reactions produced by drugs, the previous general level of the patient's temperature must be taken as the basis for comparison.

THE BODY-WEIGHT similarly, in a body which gains and losses weight, indicates merely the relationship between the katabolic and anabolic phases of metabolism. Under the conditions of rest and diet, sufficient to maintain temperature and weight at their usual levels, if the administration of a drug is followed by a loss in weight, there has been a relative increase of katabolism over anabolism; if by a gain in weight, there has been a relative increase of anabolism.

THE STATE OF NUTRITION OF THE FAT AND MUSCLES, in which occurs the bulk of the metabolism of the body, also gives an indication of the situation and character of metabolic alterations.

THE STATE OF SLEEP/

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\* "The Temperature of the Body in the Insane."  
Journ. Ment. Science. April 1868.

THE STATE OF SLEEP also has important bearings on metabolism. During sleep anabolism or tissue-repair predominates over katabolism or tissue-waste. Sleep, "great Nature's second course," is in short the chance of repair, the opportunity which the body has of making good by night what it has lost by day. Hence prolonged insomnia may end in loss of weight - there being constant wear and tear but no repair - and it is said<sup>\*</sup> to be even "more damaging to the organism as a whole than starvation. Prolonged mental excitement, by maintaining a constant excess of katabolism, similarly ends in loss of weight. Hence insomnia and mental excitement, when excessively marked, had to be borne in mind as factors capable of vitiating the balance of metabolism and the conditions of rest in bed.

Insomnia and mental excitement had always been remedied as far as possible by previous treatment.

#### FINALLY THE STATE OF THE APPETITE AND PRIMARY DIGESTION

as bearing upon the ingestion of the food and drugs prescribed, was kept under observation. Previous digestive errors had been corrected as far as possible/

<sup>\*</sup> Donaldson on "The Nervous System," Howell's American Text Book of Physiology. 1896.

possible before Animal Extracts were administered.

II. THE PULSE. According to Dr. Gaskell of Cambridge the vagus and sympathetic nerves convey impulses to the heart, which set up metabolic changes in the direction of anabolism and katabolism. Consequently the frequency of the pulse may give an indication of the state of metabolism of the heart-wall, a maintained acceleration of the pulse meaning excessive katabolism of the myocardium, a slow pulse pointing to excessive anabolism.

SPHYGMOGRAPHIC PULSE-TRACINGS (with a Dudgeon Sphygmograph) were attempted in most cases but frequently had to be abandoned owing to want of attention and cooperation by the patient. The instrument was fully wound up before each tracing so as to ensure the same rate of motion each time, and thus to put on record the actual rate and rhythm of the pulse at the time, and to avoid any fallacious alteration of the form of the curve by a paper moving at different rates on the various occasions of observation. The instrument was applied to the same radial artery in the same individual on each occasion, the spring-plate being placed just above the base of the Styloid process and exactly/

exactly over the middle of the vessel, and the eccentric wheel so graduated as to give the best range of movement with as moderate an amount of pressure as possible ( usually 2 to 3 oz.). The tracings were taken as nearly as possible at the same hour of day in each case, and with the patient in the sitting posture. Owing to the many sources of error in the taking of pulse-tracings, many observations are necessary in the case of any given drug before one can form a conclusion as to its effect on the pulse curve, and there is a good atom of truth in the saying that a pulse-tracing may be made to prove anything.

In several cases observations of the Blood-Pressure in the brachial artery were made with Hill and Barnard's Sphygmometer.

THE INVESTIGATION OF THE BLOOD had sometimes to be abandoned owing to the insane suspiciousness or restlessness of the patient. In cases where the examination was made, the finger was gently cleansed and pricked at the quick or tip, and from the drop obtained estimations were made of the Haemoglobin with a Gower's Haemoglobinometer, and of the corpuscles with a Thoma-Zeiss Haemacytometer - the 1 in 200 dilution being used. With this degree of dilution there are in health usually/

usu  
ally about 100 red blood corpuscles in man, and about 90 in woman, in a field of 16 squares. The average number of Red Blood Corpuscles in several fields of 16 squares may therefore be taken as the Haemic Unit, or percentage of red blood corpuscles to that of health.

THE AVERAGE VALUE OR WORTH OF EACH CORPUSCLE as regards its haemoglobin is expressed by the fraction in which the percentage of haemoglobin forms the numerator and the percentage of red blood corpuscles the denominator.

In the case of several drugs, film preparations of the blood were made by Dr. Lovell Gulland's method, in which the films are first fixed and stained in a mixture consisting of absolute alcohol, ether, corrosive sublimate, and eosin (which stains the <sup>h</sup>haemocytes) and then after washing are counter-stained in a saturated aqueous solution of methylene blue (which stains the leucocytes and blood-plates).

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THYROID EXTRACTS.

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## THYROID EXTRACTS.

### A. MAIN FACTS RELATING TO THE LIFE-HISTORY, STRUCTURE, COMPOSITION, FUNCTIONS, DISEASES, AND EXTIRPATION OF

#### THE THYROID GLAND.

##### (a) Life-History and Structure.

The chief facts seem to me to be (1) that the thyroid begins life early in the embryo, namely by the third week. (2) That it develops much in the same way as a simple gland, rising as it does <sup>from one median</sup> ~~from one median~~ tubular and two lateral ~~sac~~ saccular involutions of the hypoblast into the mesoblast of the embryonic pharynx, the hypoblast becoming the epithelium of the alveoli ~~of~~ the gland and the mesoblast forming the intervening stroma; the lateral sacs becoming the "lateral lobes" of the gland; and the median tube giving rise to the "isthmus", and to the "pyramid" and "accessory lobes" when present; and its orifice persisting as the "foramen caecum" on the dorsum of the tongue. (3) That the "colloid," or secretion of the gland, is formed by the epithelium of the alveoli in the usual way of gland cells, but instead of being conveyed away from the alveoli by an <sup>ex</sup>cretory duct, it transudes into the lymph spaces and lymph-vessels of the inter-alveolar stroma whence it is slowly served out to the circulation, /



lation, or it is more rapidly supplied to the system by direct reabsorption into the blood-vessels, which like the nerves of the thyroid, are rich in number and distributed immediately upon the epithelium of the alveoli

(4) That the thyroid is relatively larger in the foetus and infant than in the adult. (5) That it decreases in relative size especially during the first month after birth (\*<sup>1</sup> Krause), and slowly during the rest of life. (6) That in adults it is larger in women than in men, and enlarges frequently at menstruation and occasionally during pregnancy. (7) That in old age it deteriorates considerably in structure, becoming indurated and impregnated with earthy deposits.

\*<sup>2</sup>

(B). COMPOSITION.

The human thyroid contains in the fresh state about 80 per cent of water and 20 per cent of solids, the solids being relatively more abundant in the infant than in the adult. The solids are proteids and proteid - like substances with small quantities of extractives and inorganic salts. The proteid constituents/

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\*<sup>1</sup> Schäfer & Symington. Splanchnology. (Quain's Anatomy. 10th Edit<sup>n</sup>.)

\*<sup>2</sup> Halliburton "Chemistry of Tissues and Organs."  
 Schäfer's Physiol. Vol. I. 1898: and Physiol. and Pathol. Chemistry. Hutchison. Brit. Med. Journ. 1896. I.722, 1897. I.194.

ents consist, with the exception of a little albumin, mainly of nucleo-proteids and so are rich in phosphorus, and they are derived from the colloid matter and from the alveolar epithelium. Several active principles have been described, and it will suffice to mention the following:-

(1) Notkin and Bubnow's Thyreo-proteid, a proteid body of *enzyme nature, said to be physiologically active.*

(2) Frankel's Thyreo-Antitoxin, an extractive base, probably inert.

(3) Dreschel's Thyred Bases, two or three in number, also probably inert.

(4) Roos and Baumann's Thyro-iodin (or Iodo-thyrin), an organic compound containing iodine and phosphorus, occurring in the gland partly free but mainly mixed with proteid, from which it can be artificially separated. It is stable enough to resist gastric digestion and is said to be active, but in the hands of some it has failed, and it is said to be absent in the thyroids of children and dogs whose glands are well known to be specially active.

(5) R. Hutchison's Colloid Powder or Thyrocol, the iodine-containing colloid matter of the alveoli, as distinguished from the nucleo-proteid of their epithelium. According to Hutchison the activity of the gland is due neither to extractives nor to nucleo-proteids, but to the iodine - containing colloid matter: this is split up in the stomach into (a) a very active non-proteid/

*Hutchison. op. cit.*

proteid body which contains all the phosphorus and most of the iodine of the original colloid; and (b) a feebly active proteid body combined with the rest of the iodine. Probably the active non-proteid body is identical with proteid-free thyro-iodin, and the activity of the feeble body is probably due to some thyro-iodin not proteid-free, although Hutchison was unable to split it off from the proteid even by the use of 10 per cent sulphuric acid. Possibly the thyroid has several active principles with different actions as Dreschel has suggested, but in all probability the essential principle of the thyroid is Iodothyrim (or thyro-iodin), a non-proteid body containing iodine, and occurring in the colloid matter, combined more or less with proteid which is not essential to its actions. The sheep's thyroid which resembles man's in composition is said to contain from 0.2% to 0.5% of iodothyrim, from which it will be seen that individual sheep glands must vary much in physiological activity.

### (C.) FUNCTIONS.

The older views as to the thyroid being a blood-gland, and especially a blood-forming gland as put forward by Horsley, were dispelled by Lockhart Gibson who showed that any blood-forming function of the thyroid was merely in proportion to the amount of lymphoid tissue which it might contain. Simon, Cyon, and others/

others have suggested that the thyroid by dilatation and contraction of its large and numerous blood-vessels, can lower or raise the carotid blood-pressure and so can influence the cerebral blood supply. While this may be so the thyroid can in no way blood-let the brain, as its blood vessels do not form any anastomoses either with the internal carotids or with the vertebral arteries. The richness in vascularity of the thyroid is probably an expression of its important and essential glandular function.

The function of the thyroid is admitted by all to be to <sup>serve</sup> ~~some~~ the ultimate nutrition of the body, and especially that of the nervous system and of the connective tissues. The mode however in which the thyroid effects its purpose in the economy has been and still is the subject of considerable enquiry. Thus the thyroid may directly influence the nutrition of all tissues from the blood side, paying special attention however to the metabolism of the connective tissues and nerve-centres. Or the thyroid may primarily influence the metabolism of the central nervous system and through this the nutrition of the connective and other tissues. Or conversely the metabolic changes in the central nervous system may in part be an expression of those produced in the peripheral tissues generally and transmitted centripetally along afferent/

\* Foster's Physiology- Schafer's "Internal Secretions." Brit-Med. Journ. 1895 August 10th, and Physiol. Vol-I-1898.

afferent metabolic nerves. Or finally the thyroid may be essentially concerned with the nutrition of the connective tissues only, and consequently its function as regards the nerve-centres may be to keep the neuroglia in a healthy state so that the working of the essential nerve elements may not be interfered with.

These aspects of the modus operandi of the thyroid however have not received so much attention as the question as to whether it effects its influence upon metabolism by supplying a substance which is added to the economy and is essential to nutrition ("Internal Secretion" Theory of Schiff, Schäfer, and others), or by removing from the economy and rendering harmless, supposed toxic<sup>c</sup> products of metabolism which would by their accumulation be injurious to nutrition. (Excretion or Antotoxication" theory of Victor Horsley and others). There seems to be little doubt now that the former view is the correct one, that the thyroid forms a positive "internal secretion" which is essential to the nutrition of the nervous and connective tissues. This<sup>s</sup> is borne out by the fact that administration of thyroid extract produces distinct physiological actions in the healthy subject and relieves the effects of extirpation and of certain diseases of the organ.

(D)./

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(D). EFFECTS OF DISEASE.

Absence, atrophy or degeneration of the gland means deficiency of thyroid excretion, which occurring before birth or in early life leads to Cretinism, and occurring in later or adult life leads to myxoedema ~~dema~~ — a condition first described by Sir William Gull as "a cretinoid state supervening in adult life in women," and afterwards shown by Dr. Miller Ord to be due to an atrophic state of the thyroid. The two diseases are essentially similar, the clinical differences being entirely explainable by the period of life at which the malady sets in, in the one case before the growth and development of body and mind have fairly begun, and in the other case after they are completed. Hence in the cretin the effects upon the bones and brain are the most striking, whilst in the "cretinoid adult" the alterations in the skin and subcutaneous tissue, which are capable of more active growth are so marked as to be the source of the name "Myxoedema," it having been at first thought that the condition of these structures was one of oedema with deposit of mucin, whereas it is now known that their state is one of overgrowth of the connective tissue which is embryonic (mucoid) in type and so contains excess of mucin.

*In Exoph*  
~~An Epithalmic~~ Goitre, which in many respects is the/

the antithesis of myxoedema, the well-known research of Greenfield, who showed that the essential morbid change in the thyroid was a hyperplasia especially of the alveolar epithelium analogous to the catarrh of a mucous surface, indicate that the disease is due to excessive or perverted thyroid secretion. It is interesting to note that many of the symptoms of Exophthalmic goitre are similar to the phenomena of thyroidism, produced by large doses of the extract of the gland. Again a number of cases is now on record in which exophthalmic goitre has been followed by more or less marked myxoedema, indicating that the condition of hypersecretion may in time lead to thyroid insufficiency.

In other forms of "Goitre" there may occur a hypertrophy of all the structures of the gland (simple goitre) or more particularly of its alveoli (Cystic g.), or its stroma (fibrous g.), or its vessels (vascular g.), or a goitre may undergo calcification (calcareous g.). Or inflammation may arise in a usually already goitrous thyroid (inflammatory g.), or Sarcoma or Carcinoma may attack the gland (malignant g.). In all these forms of goitre, apart from the complications which may arise from local pressure, it is important to note that although there is enlargement of the gland present, the disease if it last long enough may more or less involve and destroy the parenchyma and so may lead to deficiency of thyroid secretion/



tion and supervention of cretinoid or myxoedematous features. Hence we may say that in any extensive disease of the thyroid, there is a tendency to the destruction or atrophy of its essential gland structure, and that if this take place to a sufficient extent while the gland is still of use to the economy, there will be deficiency of thyroid secretion and supervention of terminal cretinoid or myxoedematous features. Finally it is interesting to note the characteristic mental conditions in diseases of the thyroid; irritability and excitability and emotional instability leading to melancholia or mania, in exophthalmic goitre; mental placidity or hebetude or stupor or even dementia in myxoedema; and imbecility or idiocy in cretinism. Similarly the trophic and sensori-motor functions are characteristically affected, the hyperexcitability, tremors and tendency to pyrexia in exophthalmic goitre contrasting strongly with the sensori-motor sluggishness, low temperature, and liability to chills in cretinism and in myxoedema. These clinical facts are strong proof of the intimate relation of the thyroid to central nervous metabolism.

#### (E). EFFECTS OF EXTIRPATION.

Total Thyroidectomy in man for goitre is followed by the same symptoms as its atrophy, that is by an artificial myxoedema. The group of symptoms was first described/



described in 1882 by the Reverdins under the name of of "operative myxoedema," and in 1883 by Kocher who termed the condition "Cachexia Strumipriva," and by Mathers since under the name of "Cachexia thyreopriva." Kocher first pointed out that "operative myxoedema is most marked in young subjects, becomes less liable after thirty, and may not occur at all as age advances. Horsley has even suggested that some of the appearances of old age may be due to thyroid atrophy, but it would seem more probable that the deterioration of the thyroid in old age is just a part of the general senile decay of the organs, otherwise administration of thyroid extracts should keep an old man young, whereas as a rule thyroid extracts are badly tolerated by the old, this fact indicating to my mind that the ageing body is accustomed to less thyroid secretion than in the youth and adult, and therefore that the thyroid is not so essential to nutrition in old age. Total thyroidectomy has not been performed in children, so far as I am aware, but it would be interesting to know whether this operation would be followed by the acute nervous symptoms so commonly seen in the lower animals. Acute nervous symptoms with pyrexia and cardiac failure have been often observed by surgeons in operations on adults, but so far as I am aware only in cases of partial thyroidectomy, and these symptoms so/

so closely resemble some of those of thyroidism as to suggest that they are a form of thyroid poisoning, due not to removal of part of the gland but to a wounding of the gland during operation with consequent excessive absorption of colloid juice by the raw wound surfaces.

Total Thyroidectomy in the lower animals is followed by effects depending apparently upon the particular species order or class to which the animal belongs, and upon its age. Sometimes no effects occur at all, sometimes slow cretinid changes as in man, and sometimes there is a rapidly fatal train of nervous symptoms characterised by anaesthesia, tremors, clonic spasms, tetanic convulsions, coma and death. In <sup>case</sup> ~~three~~ animals in which thyroidectomy is injurious it may be stated generally, that the younger the animal is the more likely are the acute neurotic and fatal symptoms to occur; that in older animals, there may be a "neurotic" stage, but more commonly there are "cretinic" or "mucinoid", and ultimately "maras<sup>m</sup>enic" features; and that in old animals there may be no serious effects at all. It seems to me strange that in the sheep whose thyroid is very active pharmacologically, total thyroidectomy should be harmless. The absence of symptoms after thyroidectomy in the rabbit has been variously attributed to vicarious action by the/



the pituitary body which is large in rabbits, or to failure to remove the whole of the thyroid, or the necessary thyroids, or the parathyroids, removal of which alone is said by Gley to produce the acute effects of thyroidectomy.

The general results of thyroidectomy in animals seem to me to indicate that the gland is more essential to nutrition in younger animals, and therefore that its removal in them gives rise to more acute

Symptoms which, as has been suggested, are fatal before the cretinic features characteristic of older animals have time to appear. From this I would infer that in the younger subject there is always a good supply of thyroid secretion in the system, and in my experience young subjects, below twenty years, do not tolerate thyroid well, not because as in the old the body is accustomed to only a small quantity of the secretion, but because it already has a full supply.

B.

ADMINISTRATION OF THYROID EXTRACTS, IN HEALTH, IN  
DISEASES GENERALLY, AND IN MENTAL DISEASES.

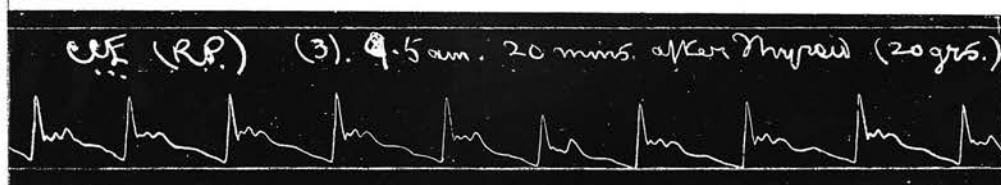
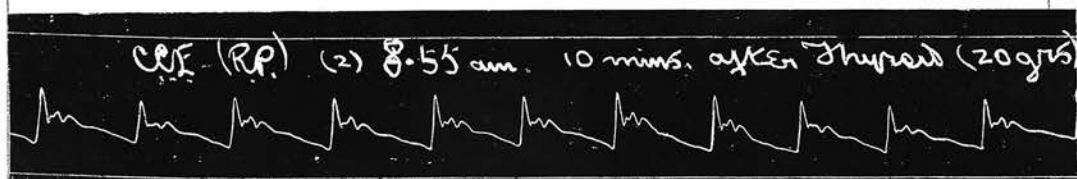
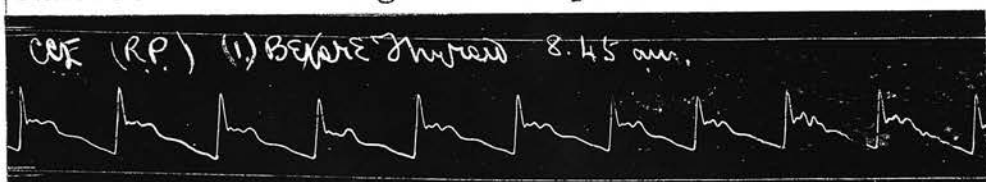
(a) IN HEALTH.

Administration of thyroid to a healthy person produces loss of weight at the expense of the fat, and so increases non-nitrogenous metabolism. The effect on nitrogenous metabolism is not so clear, but the majority of recent observers find that this also is increased, as indicated by a rise in the urinary nitrogen. During thyroid feeding in health the urine shows according to various observers an increase in water, urea, phosphates, and chlorides. Glycosuria is also said to occur, due according to Bethmann to an inability on the part of the portal circulation to maintain at its previous level the absorption of sugar, an excess of which consequently passes by the <sup>o</sup>thoracic duct into the general circulation and so is excreted by the kidneys. Large doses in health also increase the pulse rate and may produce palpitation and fainting. Oliver and <sup>e</sup>Shäfer<sup>\*1</sup> state that intravenous injection of thyroid decoction in the dog produces an immediate transitory fall of the blood-pressure, and Oliver<sup>\*2</sup> states/

\*<sup>1</sup> Journ. Physiol. Vol. XVIII. 1895.

\*<sup>2</sup> Greenian Lectures. Lancet. 13 June 1896.

states that administration of thyroid in man produces a specific dilatation of the radial artery. Hutchison<sup>\*</sup> however, states that organic extractives in general produce, when injected intravenously, a lowering of blood-pressure, but not when given by the mouth, and that the active principle of thyroid does not lower blood-pressure in whatever way it be given. A single large dose given by the stomach seems to produce no obvious effect on the pulse in health, as may be seen from the subjoined tracings on myself taken before and after a dose equivalent to a third of a sheep's gland and administered on an empty stomach. The tape of the sphygmograph was released between each tracing; no characteristic change of the pulse-curve is seen.



\* Hutchison. Brit. Med. Journ. 1898. II. p. 144.

This so far confirms Hutchison's view; but in the insane when under the full influence of the drug, a distinct lowering of blood-pressure occurs, as will be seen later, thus supporting Schafer and Oliver's view, and showing that a lowering of blood-pressure can be produced by free mouth administration of thyroid.

(b) IN DISEASES GENERALLY.

As is well known the effects of atrophy or degeneration or removal of the thyroid may be ameliorated, cured, or even prevented by the administration of thyroid, a thyroid graft, provided that it "takes" and does not become absorbed, being permanently effectual, but as this is rare, all other forms of thyroid treatment usually require to be continued permanently.

Thyroid extract is thus the specific cure for cretinism and myxoedema. It is not so beneficial in exophthalmic or in other forms of goitre, but it seems to promote the removal of the colloid from the gland in goitre, and in cases where there are also present myxoedematous features, thyroid is still more beneficial, relieving the concomitant myxoedema. Stock-  
\*  
man has ingeniously suggested that in the treatment of goitre by iodine, the latter acts by promoting the liberation /

liberation of the active principle of the thyroid from the gland, and that the toxic and fatal symptoms which occasionally arise constitute a distinct form of iodism which is more truly a severe thyroidism. He also attributes the beneficial action of iodides in atheroma aneurism and tertiary syphilis to a similar stimulation of thyroid secretion by the iodine of the drug. Thyroid has been found beneficial in obesity; in such skin affections as psoriasis, sclerodermia, warts, ichthyosis, eczema, lupus, and exfoliative dermatitis; in acromegaly and in un-united fractures; and in haemophilia. It has not given striking results in neurasthenia or in hysteria or in nervous affections generally. It has been tried in diabetes, and has been recommended for fatty but not for true or lean diabetes. It has even been tried in fatty heart, and has been recommended for fatty infiltration but not for fatty degeneration. Of course like most other remedies it has been found beneficial in amenorrhoea and metrorrhagia and other functional disorders in the female, and it has been frequently given by gynecologists for uterine fibroids and carcinoma, and after various pelvic operations. Beatson of Glasgow, and others since, have reported cases of recovery from mammary carcinoma after excision of mammae and ovaries, combined with prolonged after-treatment /



after-treatment by thyroid extract which is held to be an essential part of the cure. Thyroid has also been tried in prostatic diseases in the male, and also in chronic nephritis and renal inadequacy, in order to promote the <sup>ex</sup>secretion of urea.

(c) IN MENTAL DISEASE.

The mental symptoms of myx<sup>ε</sup>odema and exophthalmic goitre are so pronounced as to constitute distinctive features of these diseases, and they may become so aggravated as to pass into insanity, the insanities of myx<sup>ε</sup>odema and goitre. It was not to be wondered at therefore that, after the discovery of the thyroid cure for myx<sup>ε</sup>odema by Murray and Horsley in 1891, the new remedy was applied to the treatment of these forms of insanity. In 1892 <sup>\*1</sup> G. Macpherson described the cure of both the myx<sup>ε</sup>odema and the insanity in a case of myx<sup>ε</sup>odemic insanity treated by thyroid grafting, and he was followed by other physicians who reported the recoveries of myxoedemic patients under their care who in many cases had been long and apparently incurably insane. In 1894 T.S. Mc.Claughran <sup>\*2</sup> reported recovery and improvement in two cases of insanity with goitre treated with thyroid extract. In 1893 however L.C. Bruce and S.R. MacPhail, noticing /

\*<sup>1</sup> Edinr. Med. Journ. May 1892.

\*<sup>2</sup> Journ. Ment. Scien. Oct. 1894.



ing in the descriptions of the thyroid treatment of myx<sup>e</sup>odema the production of a febrile reaction by the drug, and remembering the frequent recoveries of insane patients after attacks of fever and inflammations, found that a feverish condition could similarly be produced in the insane by the use of large doses of the drug, and so they applied thyroid in large doses to the treatment of the insanities generally, hoping to stimulate Nature's method of cure in such cases, and by inducing a febrile process to get the benefit of the subsequent stimulus to nutrition. Their efforts were so successful therapeutically as to attract the attention of alienists generally. Bruce in his subsequent papers was inclined to attribute the beneficial effects of thyroid in insanity not only to its general stimulation of nutrition as in fever but also to a specific excitant action on the brain cortex. In December 1894 I administered thyroid, according to Bruce's method, in a case of chronic insanity of over  $2\frac{1}{2}$  years' duration, with a history of acute peripheral mania followed by stupor, and apparently drifting into dementia. The patient made a remarkable recovery. I decided to make an extended trial of the drug in the various forms of insanity, /

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\* Bruce and MacPhail. "Thyroid Feeding in Insanity." Galedonian Med. Journ. October 1894: and Lancet 13 Oct. 1894.

Bruce Journ. Ment. Scien. Janr & Octob. 1895.  
& Edinr. Hosp. Reports 1895 & 1896.

insanity, and during the past five years I have administered thyroid in 120 cases, a larger number of personal cases than has hitherto been recorded. During these years many physicians have published their results, and the literature of the thyroid treatment of insanity is already extensive. The differences in the results of various observers are extraordinary, the percentages of recovery varying from 0 per cent to 50 per cent in the different records. Two American physicians have recently given a summary of over a thousand cases collected from the literature and elsewhere. These cases include (1) 485 published cases in the literature, yielding 23.9% recovered, 29.4% improved, and 46.6% unimproved. (2) 508 cases treated in the United States and Canadian Asylums, all of which had a circular sent to them by the authors requesting their results in thyroid treatment, and thirty-six of which responded. These 508 hitherto unpublished cases yield 9.8% recovered, 18.5% improved, and 71.6% unimproved. (3) 39 additional cases treated by Maben and Babcock themselves, yielding 19.8% recovered, 26.2% improved, and 54.0% unimproved. Collectively/

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\* Maben & Babcock. American Jour. Insan. Octob. 1899.

Collectively the 1032 cases yielded 16.8% recovered, 24.0% improved, and 59.2% unimproved. It must be confessed however, that notwithstanding these very fair results on paper, the majority of alienists are at present somewhat disappointed with their experience of thyroid treatment in insanity, and J. Shaw <sup>X</sup> has recently expressed this feeling somewhat pessimistically, when he states that "thyroid can hardly, after some 'years' trial, be said to be reliable(in insanity) except in myxedematous and cretinoid cases, but it appears often to act well in melancholia and stupor." There must be a reason for this aspect of opinion, and it seems to me to be this. After carefully reading the published cases which, we may take it, are more often the good than the poor results, I feel convinced that many of the reported recoveries were not fair tests in the sense that thyroid was employed when there was still a good chance of recovery by the ordinary methods of treatment. Where one desires to ascertain and to test the therapeutic value of a drug in disease the drug should not be employed until the disease is distinctly seen to be making no progress towards recovery under the usual modes of treatment, and until therefore one can distinctly say that the prognosis is/

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\* The Medical Annual. Art. Insanity. Bristol & Lond. 1900.

is not good or not so good as it was. In the case of the more hopeful forms of insanity, the practical test of prognosis from this point of view is usually the prolonged duration of the illness in spite of active treatment before and after admission to an asylum. In the report of any case of insanity treated in an asylum with a special drug, there should therefore always be <sup>made</sup> a definite statement of the duration of the disease firstly before and secondly under asylum treatment. Most ordinary recoveries in asylums occur within the first three or six months after admission, but in some cases of insanity one is not justified in waiting all this time before applying special drug treatment, if the special features of the case show the prognosis to be not good. To give thyroid however in a hopeful and curable case of insanity of only two or three months' total duration or when it has been barely a month under asylum treatment, makes no advance in solving the problem of the ultimate curative value of thyroid in insanity. I do not for a moment deny that thyroid promoted recovery in the cases reported, but when a drug is on its trial therapeutically, its too early employment in the distinctly curable stage of the disease, yields an unduly high percentage of recoveries and in the end will lead, as it has done in the case of thyroid, to disappointment when the drug comes to be used /

used in similar cases where the prognosis is not so good, and consequently will lead to disparagement of what may really be a useful drug. Once that the therapeutic value of a drug is established, by all means let it be used to promote recovery in any stage of the disease if it will do so better than other remedies. When a drug however is on its trial for its therapeutic effects, it should only be employed in cases in which ordinary remedies have distinctly been proved to be ineffectual. A recovery under these circumstances almost amounts to a cure, and the therapeutic value of the drug is at once established. The total results in a series of such cases may not perhaps be so brilliant as they might have been, but they are a truer approximation to the actual capabilities of the drug in question.

The following is an account of the pharmacological actions and therapeutic uses of thyroid in my own cases.

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PHARMACOLOGICAL ACTIONS OF THYROID EXTRACT

IN THE INSANE.

The pharmacological actions of thyroid extract in diseases markedly involving the mental functions have been well described by Byrom Bramwell in relation to cretinism and myxoedema, and by Bruce and Macphail\* and others in the case of the insanities generally. The chief value of the following observations is that they are based on a large number of cases - namely on 120 separate administrations of the drug - and consequently they enable me to state the actions of the drug in the insane with more precision, and also to contribute a little fresh knowledge on the subject. The Forms of thyroid extract which I have employed included the officinal preparations "Liquor Thyroidei" and "Thyroid-eum Siccum;" the powder "Thyrocol" which is identical with Dr. Hutchison's "Colloid Powder," and is prepared according to his method by Messers Oppenheimer Son & Co, London; and the "Thyroid Tabloid" of Messers Burroughs Wellcome & Co., London and Sydney. All of these preparations are obtained from the sheep, whose thyroid/

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\* Edinr. Hosp. Reports. 1395.

Op. Cit.

thyroid in the fresh and healthy state weighs on an average 60 grains (4 Gm. approx) and contains from 0.2% to 0.5% of iodothyron - a considerable variation, depending apparently upon the age of the animal. In the pharmacopeial preparations no restriction is put on the age of the sheep from which the thyroids are obtained, but Messrs. Burroughs Wellcome & Co. inform me that they employ only young thyroids as these are more uniform in bulk and in activity. I have found the Tabloids very reliable and uniform in action, and from their convenience of administration have used them more extensively than the other preparations. Only fresh preparations were used in all cases. Liquor Thyroidei is a glycerine extract of thyroid containing phenol and distilled water. Thyroideum Siccum is obtained by drying the glands at from 90° to 100° F. and purifying with petroleum spirit to remove fat. Thyrocol is the colloid matter freed from proteids and extractives. Thyroid tabloids are made from the whole substance of the glands, dried at a uniform temperature of 100° F., and, with the addition of Sodium chloride, lightly compressed. Each tabloid weighs 5 grs., and is equivalent to 5 grs. of the fresh gland.



All of these preparations are physiologically active, and all of them are capable of producing similar undesirable effects upon the heart, stomach and nervous system, and these effects are <sup>the</sup> toxic phenomena of thyroidism, and are not in my opinion attributable to impure or useless substances in the preparations. As regards their relative physiological activities in the insane, taking as a standard of comparison the fresh and healthy young gland of the sheep, which has an average weight of 60 grains, I would say that usually 1 gland (weighing 60 grains) equals 100 minims of Liquor Thyroidei, equals 60 grains of Thyroideum Siccum, equals 60 grains of Thyroid Tabloids, equals 20 to 15 grains of Thyrocol. According to Hutchison an average gland yields one tenth of its weight of Thyrocol, that is about 6 grains, but I have frequently used three times this amount (i.e. 18 grains) and found it to correspond in activity to only one gland. Thyrocol however is a concentrated preparation in comparison with the others, and in my experience is three or four times stronger than the "tabloid" or than "dry thyroid", and five or six times stronger than "thyroid solution."

The drug in all cases was administered by the stomach/



stomach, it having been long established that this site of administration ensures the <sup>its</sup> efficient action of ~~thyroid extracts~~.

The Doses employed were large (92 cases), moderate (8 cases), small (15 cases), and varying from small to moderate and finally to large (5 cases). Physiological reactions are producible with any size of dose repeated sufficiently often and long, but I desired to ascertain whether good therapeutic results could be obtained in the insane with other than large doses, as this comparative method of administration might give an indication of the *raison d'être* of the value of thyroid extract in insanity.

I.                      LARGE DOSES. (92 CASES).

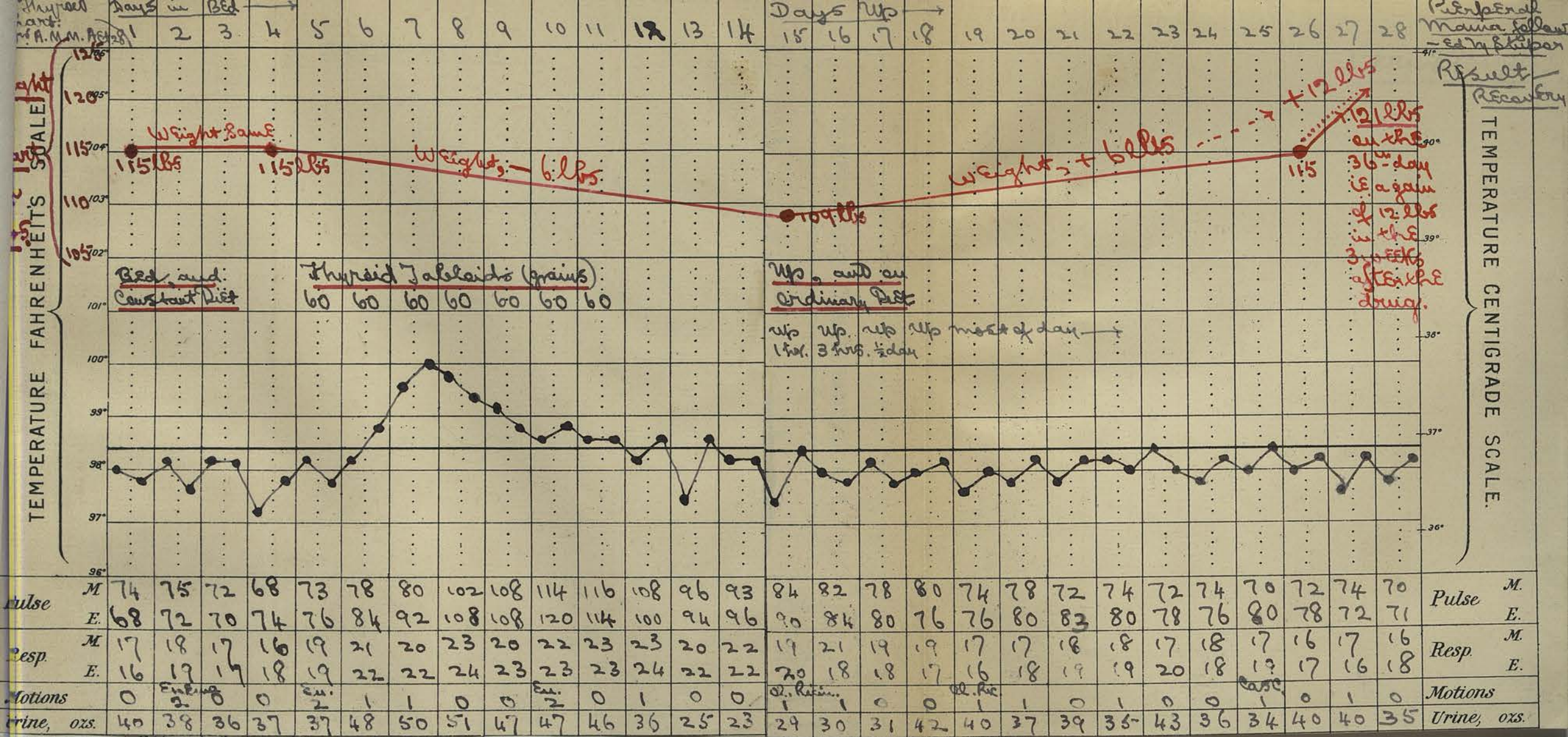
In the great majority of my cases the large doses originally recommended by Bruce were used. Here the object is to rapidly produce the full physiological effects of the drug and a certain degree of thyroidism, the administration being pushed until a definite reaction occurs and toxic symptoms supervene. Thyroidism was usually produced in my cases by giving the equivalent of a young sheep's thyroid daily for a week. This usually meant a daily dose of 90 to 100 minims of Liquor Thyroidei (e.g. 30 m.T.i.d.), or 60 grains of Thyroideum/

Thyroideum Siccum, or of 60 grains of Thyroid Tabloids (20 grs.T.i.d.), or of 15 to 20 grains of Thyrocol (e.g. 6 grs.T.i.d.), continued for six seven or eight days. The majority of the patients had within a week 420 grains of dry thyroid extract in "tabloid" form. Sometimes the patient began with a daily dose of two-thirds of a gland, increased later to one gland, or even to one and a half glands (e.g. 90 grains of tabloids), and although the period of administration in the case of the large doses was usually a week, it lasted only two or three days in a few susceptible cases, and nearly two weeks in the case of a few patients who seemed able to take the drug with impunity.

The physiological effects produced in my cases by large doses of thyroid were as follows. (See Chart next page.)

(1) BODILY TEMPERATURE. Pyrexia was produced in the great majority of cases, this under the conditions of rest and diet being presumptive evidence of an increase of metabolism with katabolism in excess of anabolism. Pyrexia was absent in 15 per cent of cases; and present in 85 per cent, being "subfebrile" (that is, a rise of  $1^{\circ}$  to  $2^{\circ}$  F. above the previous average temperature of the patient) in 69 per cent, "slightly febrile"/





THYROID CHART 1.

febrile" (a rise of 2<sup>0</sup> to 3<sup>0</sup> F,) in 12 per cent, and  
"moderately febrile" (a rise of 3<sup>0</sup> to 4<sup>0</sup> F.) in the  
remaining 4 per cent of cases. Of the 69 per cent ~~of~~  
subfebrile cases, 50 per cent were good reactions, that  
is/



is a more or less sustained or continuous rise of between  $1^{\circ}$  and  $2^{\circ}$  F.; and 19 per cent were poor subfebrile reactions with a more or less sustained rise of only  $1^{\circ}$  F. Hence the pyrexia produced by thyroid in large doses is characteristically a good subfebrile pyrexia, that is in comparison with the general level of the previous temperature which in most cases was subnormal. In typical cases the temperature began to rise on the second evening of the drug, gradually reached its maximum, and then began to fall again on the 4th or 5th day, notwithstanding the continuance of the drug even for several days longer. This would seem to indicate that thyroid in large doses stimulates metabolism so briskly that heat-loss is unable at first to cope with the excessive heat production, but later on the highly flushed and perspiring skin is able to do so, and consequently the temperature falls although the increased metabolism continues. When the febrile reaction had obviously come to an end, the drug was usually ceased, but more frequently the latter had to be stopped on account of toxic symptoms before the temperature had reached the normal level. In many cases the pyrexia continued after the stoppage of the drug, and in a few cases a secondary pyrexia of subfebrile/

subfebrile type set in after the initial fever and sometimes was the more pronounced of the two. In less typical cases the pyrexia was irregularly intermittent instead of being continuous, and the rise of temperature might occur on the first day or not till the third or later. In a good proportion of the cases the general level of the temperature previously subnormal remained more nearly normal after the treatment.

(2) BODY-WEIGHT. A loss in weight was constant in all cases weighed within four days of the cessation of the drug, and it amounted on the average to 6 lbs; that is, a sheep's thyroid or its equivalent given daily for a week produced a loss in weight at the rate of nearly 1 lb. a day. The loss in weight amounted in the various cases to from 1 lb to 25 lbs, there being no common features amongst those who lost lightly or amongst those who lost heavily.

The loss was usually followed after the cessation of the drug by a gain in weight which was not so rapid as the previous loss but usually exceeded it in amount, the gain often doubling and sometimes trebling the loss. One of the patients who lost 6 lbs. during the drug actually gained 46 lbs. in the following 9 weeks. The gain in weight usually set in during the first/

first or second week after the drug, but sometimes not for a month or longer and in a few cases not at all. Under the conditions of rest and diet the loss in weight during thyroid feeding indicates a great excess of katabolism over anabolism, and the gain afterwards points to a powerful anabolic reaction.

As a rule there was a direct relationship between the degree of the pyrexia and the loss in weight, but loss in weight was the more constant and essential feature, and it was considerably above the average in several of the cases in which there was no pyrexia. The absence of pyrexia therefore was no proof that a reaction was not occurring.

3. INTEGUMENTARY SYSTEM. Perspiration was usually increased, generally from the third day onwards, in most cases giving rise to an increased moist feeling of the skin and in many cases being visibly profuse. This means a considerable increase in the loss of water and also, as already indicated, of carbonic acid and of urea by the skin. The loss of urea I verified in several cases. The skin during the drug was usually flushed and hyperaemic. This vascular dilatation may merely be that which generally accompanies sweating, but/

but probably it is also due to a specific dilatation of the cutaneous arterioles by full doses of the drug. A fine desquamation was not uncommon during or more often after the drug; and very frequently the skin, previously muddy and unhealthy looking, became fresh and clear after treatment. Previous skin eruptions however, such as acne, were not much benefited by thyroid in large doses. In one case an attack of urticaria, involving the whole body and accompanied by a good subfebrile pyrexia and by marked uraturia, occurred a fortnight after the drug. Haematoma auris appeared in one case during the taking of the drug, apparently spontaneously and without any causal relation to it. No changes occurred in the hair or nails. The subcutaneous fat was obviously diminished in most cases by the drug, and indeed the combustion of fat during thyroid feeding is probably the main cause of the loss in weight and the chief source of the increased output of carbonic acid and water. After the cessation of the drug fat was usually laid on, this accounting largely for the subsequent gain in weight.

(4) LOCOMOTORY SYSTEM. The bones joints and muscles exhibited no clinical changes apart from certain sensory/



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sory and motor nervous phenomena to be presently mentioned, and an incapacity for physical exertion.

(5) HAEMOPOIETIC SYSTEM. The changes in the blood during thyroidism in my cases were by no means constant or striking. Pallor was common after the drug, and was due partly to a slight anaemia but also in my opinion to the marked temporary weakening of the heart and circulation by thyroid in large doses. The examinations of the blood yielded varying results. The most common change was a diminution in the haemoglobin, but this was not constant. The red blood corpuscles were usually decreased, but in some cases were unaffected or even slightly increased. A slight degree of leucocytosis was present in the majority of the cases, affecting chiefly the small mononuclear cells. In stained film preparations the blood plates were seen to be slightly increased. The following estimations of the red blood corpuscles and haemoglobin in four out of twelve cases examined are representative of the rest, and they indicate that anaemia of the blood is not a constant or marked feature of thyroidism. After the cessation of the drug however, a tonic was prescribed which usually contained iron in order to counteract any slight anaemia present.

CASE I./

		RBC per c.mm.	Hb. %
Case I. E.H.	on day before thyroid	4,200,000.	82.
Shows Hb -	on 7 <sup>th</sup> day of drug	5,000,000	80.
but R.B.P. +	on 5 <sup>th</sup> day after drug.	4,800,000.	74.

		RBC per c.mm.	Hb. %
Case II. C.L.A.H.	Day before thyroid.	4,000,000.	80.
Shows Hb -	on 6 <sup>th</sup> day of drug.	5,000,000.	76.
but R.B.P. +			

		RBC	Hb.
Case III. E.F.T.	on day before thyroid.	4,000,000.	60
Shows Hb +	on 6 <sup>th</sup> day of drug.	3,600,000.	60
same, but R.B.P. -			

		RBC	Hb.
Case IV. M.A.C.	on day before thyroid,	4,400,000.	66
Shows Hb -	on 5 <sup>th</sup> day of drug.	4,000,000.	60
R.B.P. -			

No obvious changes were detected in the thyroid, spleen or lymph glands during thyroid treatment.

(6) NERVOUS SYSTEM. Alterations of the nervous and mental functions were frequently observed, and sometimes they were such as to necessitate the stoppage of the drug.

(a) Sensory Symptoms in the form of headaches, pains in the eyes, back, bones, joints and limbs, and tinglings pricklings and prickings in the limbs and body generally were very common, from the second or third day onwards, and were sometimes so distressing as to call for relief, the synthetic analgesiacs (as exalgine and phenacetin) usually being effectual.

(b) Motor phenomena in the form of tremors of the tongue face fingers and limbs were also common, and later there was distinct motor weakness and a feeling of great exhaustion.

(c) Reflex Excitability was occasionally increased during the earlier stage of the drug, as evidenced by an exaggeration of the patellar tendon reflex and by an increased response on tickling the soles of the feet or the sides of the body.

(d) Nutritive functions. Vasomotor flushing and sweating/

sweating and feelings of heat were common during treatment. In the later stages trophic power was temporarily reduced in some cases, as evidenced by a tendency to the formation of boils, but after treatment it was generally much improved as indicated more particularly by the healthier appearance of the skin and by the firmer condition of the muscles.

(e) Mental Excitement was common, varying from quiet talkativeness or mild restlessness to noisy scolding and impulsive acts. Thus a quiet respectable ageing melancholic who had formerly kept lodgings for medical students and who frequently helped the nurses with the dusting and tidying up of the ward, astonished us by getting out of bed and smashing some ornaments. A stuporose dement got up and danced a breakdown by her bedside, she not having been known to dance for years. Some maniacal patients became more excited and destructive during treatment. Emotional excitement of the nature of hysterical crying, or more often of smiling giggling and laughing occurred in a few cases. Temporary mental exhilaration was produced in a stuporose woman who ate 200 grains of tabloids (accidentally left by the nurse at the bedside), but/

but this passed off without further complications after the stomach had been evacuated.

Another stuporose patient became maniacal on two occasions after thyroid feeding. Towards the end of treatment some degree of mental irritability depression and confusion was occasionally seen, but it had more the character of the irritability of weakness, as if the previous mental stimulation by the drug had gone on to the stage of exhaustion.

These effects on the nervous and mental functions occurred equally in the cases without and with pyrexia, proving to my mind <sup>that</sup> the excitant action of thyroid on the nervous system is not dependent on a febrile effect alone.

(f) The Sleep function was not specially affected except in cases where the sensory disturbances were very pronounced. Neither the insomnia nor the mental excitement when present was sufficient in itself to produce a loss in weight.

(g) Circulatory System. Tendencies to palpitation and Syncope occurred in a few patients who tolerated the drug badly or who were allowed up too soon after treatment. In two cases also in which owing to the/

the absence of pyrexia it had been suggested to try the effect of hot drinks hot bottles and extra blankets, palpitation breathlessness and nervous anxiety supervened and were sufficiently alarming to make me very doubtful as to the advisability of this procedure.


THE PULSE (see Chart) was invariably increased in *rate*, usually by 30 or 40 beats per minute with large doses, but the increase varied from 10 to 60 beats in the various cases. The increase in rate generally became evident on the second day of the drug, and at this stage the pulse became more forcible and bounding and larger, resembling somewhat in character the pulse of *sthenic* fever. Later the pulse became irregular, weak, soft and easily compressible, and in the majority of cases it was the pulse which gave the signal when the drug had to be stopped. Sometimes it continued to increase in rate after the cessation of the drug, and usually in any case it remained fast *at least* for a week ~~at least~~ afterwards, and sometimes for a fortnight or even longer. The acceleration of the pulse was usually the first sign of reaction to the drug, and in my opinion is due to a stimulation of the acceleratory sympathetic centre in the medulla. Such an/

an acceleration of the heart as occurs in thyroidism would according to Gaskell's teaching point to an excessive katabolism of its substance, and the fact that thyroid powerfully promotes the combustion of fat seems to me to explain the special risk of cardiac failure in cases of fatty degeneration of the heart under thyroid treatment. There is excessive oxidation, molecular disintegration, and exhaustion of the heart-wall. In the case of a stout alcoholic female of 60 years with glycosuria, signs of cardiac failure set in at the end of treatment and were apparently being successfully combated with strychnine, strophanthus and whiskey, when unfortunately she passed from a state of stupor to one of excitement and succumbed from exhaustion. This was the only one of my cases in which a fatal issue occurred after the use of thyroid, and at the post-mortem examination, when the heart was found to be very pale soft and feeble and in a state of advanced fatty degeneration. Several patients who were the subjects of chronic valvular disease of the heart stood the drug well, but generally in these cases whisky and a cardiac tonic were administered during treatment.

Pulse-tracings showed distinct evidence of lowered/  
ed/

ed tension or blood-pressure, the crest of the curve becoming sharper, the predicrotic wave diminished, and the dicrotic wave increased. The tracings also showed distinct evidence of an increase in the dilatability or extensibility and laxity of the arterial wall, for notwithstanding the undoubted weakening of the pulse by thyroid, the height of the ascent of the curve was usually increased. Hence the lowering of blood-pressure during thyroidism is probably due partly to weakening of the heart wall and partly to increased dilatation and laxity of the arteries. Subjoined are tracings from two cases, one of melancholia, and for the sake of contrast, one of mania.

Case 1. (E.H.) Simple Melancholia.




Miss H. 10/3/98. L. Pulse. 11 am. Before Thyroid

- (1) Before thyroid, shows increased Blood-Pressure,  
Common in Melancholia.



Miss H. 17/3/98 10.30 am. L. Pulse. During Thyroid

- (2) During thyroid (7th day) shows increased rate and  
lowered tension.



Miss H. 23/3/98. L. Pulse. After Thyroid stopped

- (3) After thyroid (6th day). Shows still increased rate  
and lowered tension.



Case II. (M.R.C.) Simple Mania.

M.R.C. Before Thyroid. R.P. 9 km. P. 202. March 1900.



- (1) Before thyroid. Shows slightly lowered tension,  
Common in Mania.

M.R.C. during Thyroid (4<sup>th</sup> day of drug). R.P. 9 km 202. (April 1900)



- (2) During thyroid. Shows lowered tension, and ascent  
increased though pulse weakened.

Observations with the Sphygmometer in five cases similarly indicated a diminution of Blood-Pressure during the drug, amounting in the various cases from 40 to 30 millimetres of mercury.

(8) RESPIRATORY SYSTEM. Thyroid in large doses produced a constant increase in the Respirations, the increase amounting usually to six respirations per minute and varying from two to ten in the different cases (See Chart I.) Under the conditions of rest in bed and diet and the lungs being healthy, this respiratory increase is very significant, expressing as it were the state of the inner respiration in terms of the outer respiration. As an increase of even 1 respiration per minute means 1440 additional respirations in the

24 hours, it is obvious that the marked increase in the respirations during thyroid feeding points to a remarkable increase in tissue oxidation and to an exaggerated ingress of oxygen and output of carbonic acid and water. Judging from the acceleration of the breathing one would say that tissue respiration or oxidation is increased on an average by a fourth or third of its former ~~state~~ state of activity by large doses of thyroid. Bruce pointed out that thyroid given in large doses to patients with quiescent phthisis pulmonalis, had the effect of immediately lighting up the disease. Consequently I did not prescribe the drug in any case in which phthisis pulmonalis could be detected. However ten of my cases were tubercular, as evidenced by the presence of tubercular gland <sup>c</sup>icatrices and other signs of the Strumons<sup>us</sup> diathesis or by an after history of active tubercle at a period considerably subsequent to that of thyroid treatment. None of these tubercular cases seemed the worse of thyroid treatment. All without exception, though temporarily reduced by the large doses, ultimately <sup>Ed</sup>gaining in weight and in nutrition generally. Hence the aggravation of quiescent pulmonary phthisis by thyroid in large doses is probably due not to any specific action on the tubercle bacillus, but to the temporary reduction of/

of the nutrition and resistive power of the patient, in virtue of which the bacillus gets a better chance. Thyroid in large doses is certainly contra-indicated in all wasting diseases, such as phthisis, in which there is a tendency to emaciation and exhaustion. None of these tuberculous <sup>or</sup> cases seemed the worse of thyroid thyroid, all without exception, though temporarily reduced by the large doses, ultimately gaining in weight and in nutrition generally. Hence the aggravation of quiescent pulmonary phthisis by thyroid in large doses is probably due not to any specific action on the tubercle bacillus, but to the temporary reduction of the nutrition and resistive power of the patient in virtue of which the bacillus gets a better chance. Thyroid in large doses is certainly contra-indicated in all wasting diseases such as phthisis, in which there is a tendency to emaciation and exhaustion.

#### (9) ALIMENTARY SYSTEM.

The Appetite was generally diminished during Thyroidism, but after the treatment it greatly increased, causing the patient to eat more, lay on fat and so increase in weight. The thirst was commonly increased towards the end of treatment and for a day or/

or two afterwards. In about 25 per cent of cases the digestion was deranged by the drug in large doses, from the third or fourth day onwards, the symptoms being anorexia, inability to take or to properly digest food, bad taste in the mouth, furred tongue, nausea, vomiting, and in some cases also biliousness - with yellowish sclerotics, brownish tongue, greenish vomit, and slight choluria. Thyroid dyspepsia in my opinion is due to a catarrhal irritation of the stomach and duodenum by the active principle of the drug - possibly by the iodine of the iodothyrim. It occurred equally with all the preparations of the drug used, and was a toxic effect which necessitated its stoppage in 10 per cent of the cases and vitiated any observations on metabolism. It indicates the necessity for a comparatively simple diet during thyroid feeding.

THE ACTION OF THE BOWELS (See Chart I.) was but little influenced by thyroid in my cases, being temporarily improved in only 5 per cent of cases; but in insane women, who formed the great majority of my patients, constipation is a marked feature and is usually very untractable. In three cases, in which thyroid dyspepsia was marked and was accompanied by biliousness, diarrhoea occurred, being probably due to a downward extension of the irritation of the bowel by the drug.

(10) URINO-GENERATIVE SYSTEM.

Menstruation was frequently more profuse than usual at the regular periods; in three cases it appeared irregularly during thyroidism; and in one patient an amenorrhoeic adolescent of 20 years, it re-appeared after treatment and became regular. In another patient, an idiot of 21 years, with cretinoid features, to whom the drug was being given in small doses of one tabloid daily, menstruation appeared for the first time in the patient's life on the 26th day of treatment, but it did not recur. In several patients with uterine fibroids or cystic ovaries, thyroid in large doses produced no obvious effect on the disease.

The URINE was carefully investigated, the 24 hours' discharge being collected mixed and measured, and examined fresh the next morning.

The daily amount during thyroidism was usually increased, the increase amounting on the average to from 6 to 8 or 10 ounces, but varying to some extent inversely with the perspiration. On an average the urine was increased by a fifth of its previous amount, e.g. from 40 to 48 oz. Turbidity was common. The mucous deposit was not increased as is said to occur in myxoedema during thyroid treatment. The colour was frequently deeper, but the urine pigments were not/

not investigated. the odour was not noticeably affected. The Specific gravity was usually somewhat increased even when the urine was more abundant. The chemical reaction was almost invariably acid, but the total acidity was not estimated. Temporary slight albuminuria was produced in fully 10 per cent of the cases. Glycosuria was not met with in any of my patients, except in one, an alcoholic diabetic, in whom the sugar was increased by the drug. The absence in my cases of the "alimentary glycosuria" of thyroid feeding, was probably due to the fact that the diet prescribed did not contain an excess of sugar.

URATURIA was a common feature, and suggested that thyroidism, like fever and muscular exercise, powerfully promotes the removal from the system of the transition products of nitrogenous metabolism. It also pointed to a previous sluggishness or want of tone in the metabolism of the patients, for it has  
\*  
been shown by Noel Paton and others that muscular exercise/

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\* "The Influence of Muscular Work & Sweating & Massage on the Metabolism." Journ-Physiol. Vol. XXII.1897.

ercise produces a much greater elimination of uric acid in the case of a person who is out of condition than in the case of one who is in training. Choluria, previously present in slight degree in a few cases, was produced by thyroid mainly in the cases in which biliousness had arisen. The chromogens of indigo-red and urorosein were usually increased. Haematuria of menstrual origin alone was met with. Pyuria did not occur.

The total dissolved solids of the urine were markedly increased during thyroidism, and were estimated in the rough but with sufficient accuracy for comparative purposes by multiplying the last two figures of the specific gravity by the number of ounces passed in the 24 hours. This formula gives the total daily solids in grains, and, employed throughout a large number of cases, it indicated that the total daily solids in the urine during thyroidism were generally increased by a fourth of their previous amount (e.g. from 1000 to 1250 grains), and in the different cases by as little as one-eighth to as much as one-third of the previous quantity.

The urinary urea was much increased, more especially in the later stages of thyroidism, the increase amounting/



amounting on the average to one fourth of the previous quantity (e.g. from 360 to 450 grs.), but varying in the different cases from one-sixth to one-third or more of the original amount.

The phosphoric acid of the urine also was distinctly increased, from the commencement of the drug onwards, and the increase was usually to the extent of one-third of its previous amount (e.g. from 40 to 53 grs.) but varied in different cases from one-fourth to one-half of the original quantity. This increase in the phosphoric acid in the urine during thyroidism was most noticeable during the occurrence of the nervous and mental symptoms produced by the drug, and consequently I am inclined to attribute it partially if not mainly to an increased oxidation of the phosphorised constituents of the nerve centres.

It must be remembered that thyroid extracts consist largely of nucleo proteids and so are rich in nitrogen and phosphorus, but the amount of proteid supplied in the drug is quite insufficient to account for the increase either of the nitrogen or of the phosphoric acid in the urine. Subjoined are the daily estimations of the urine in two typical cases. (See Table I.D.R. next page.)

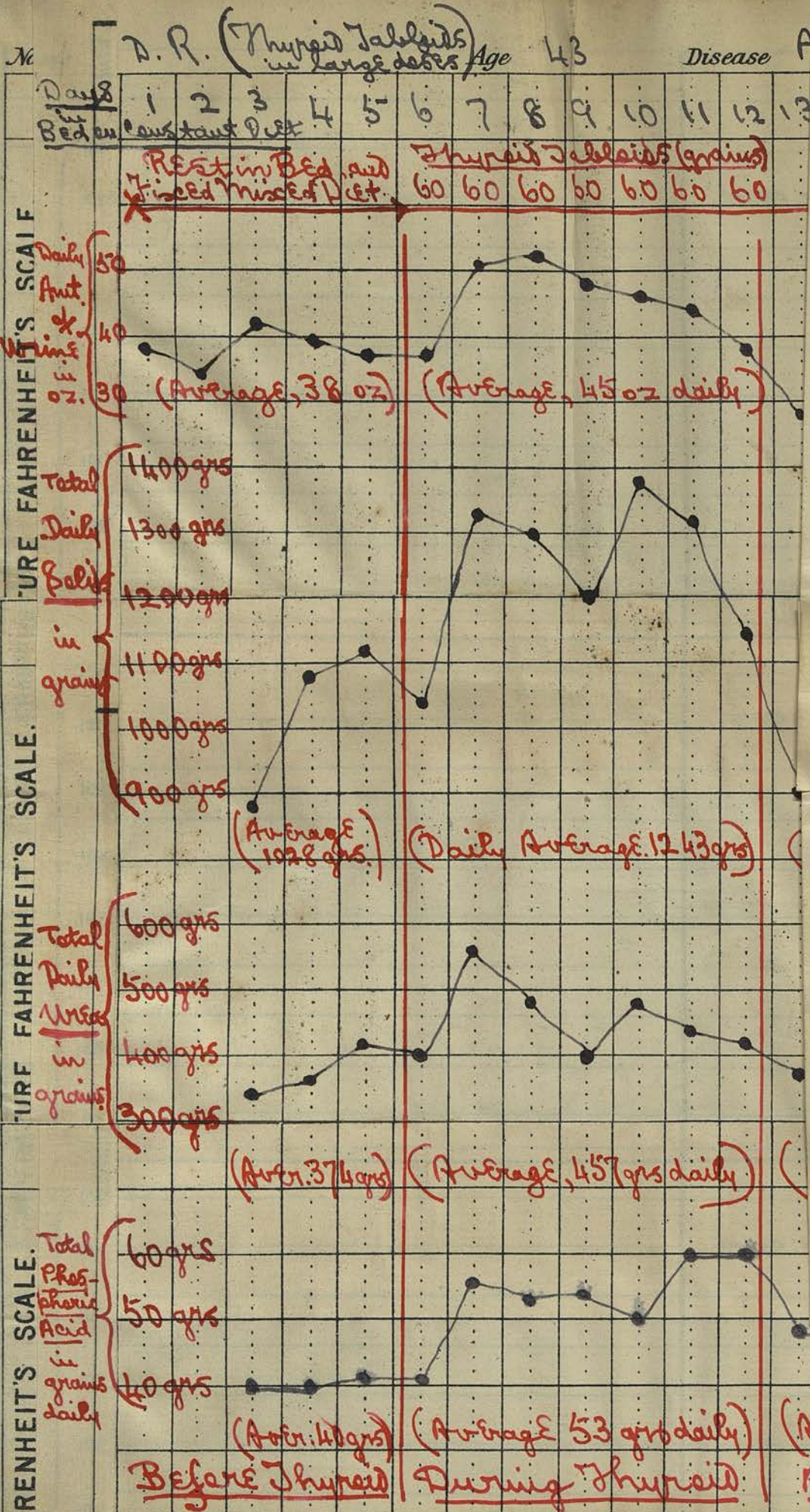


TABLE I. D.R. Aet. 43.

Case of Alcoholic Melancholic Stuper

Day in Bed.	Amount of Urine (oz.)	Specific Gravity.	Total Solids (grs.)	Total Urea (grs.)	Total Phosphoric Acid (grains)
1 Fixed diet cup? daily.	38	—	—	—	—
2 "	34	—	—	—	—
3 "	42	Daily Aver. 1021	882	343	40
4 "	39	1028	1092	358	40
5 "	39	1030	1110	421	41
6 Mynaid Tablets, 60 grs.	37	1028	1036	407	41
7 do.	51	1026	1326	561	56
8 do.	52	Daily Aver. 1025	1300	478	53
9 do.	48	1025	1200	398	54
10 do.	46	1030	1380	483	50
11 do.	44	1030	1320	444	60
12 do. (Stop)	38	1032	1140	432	60
13 Fixed diet	28	1032	896	369	48
14 "	30	1032	960	386	46
15 "	40	Daily Aver. 1024	960	372	46
16 "	36	1026	936	398	43
17 "	34	1028	952	360	41
18 Ordinary diet begins	—	—	—	—	—



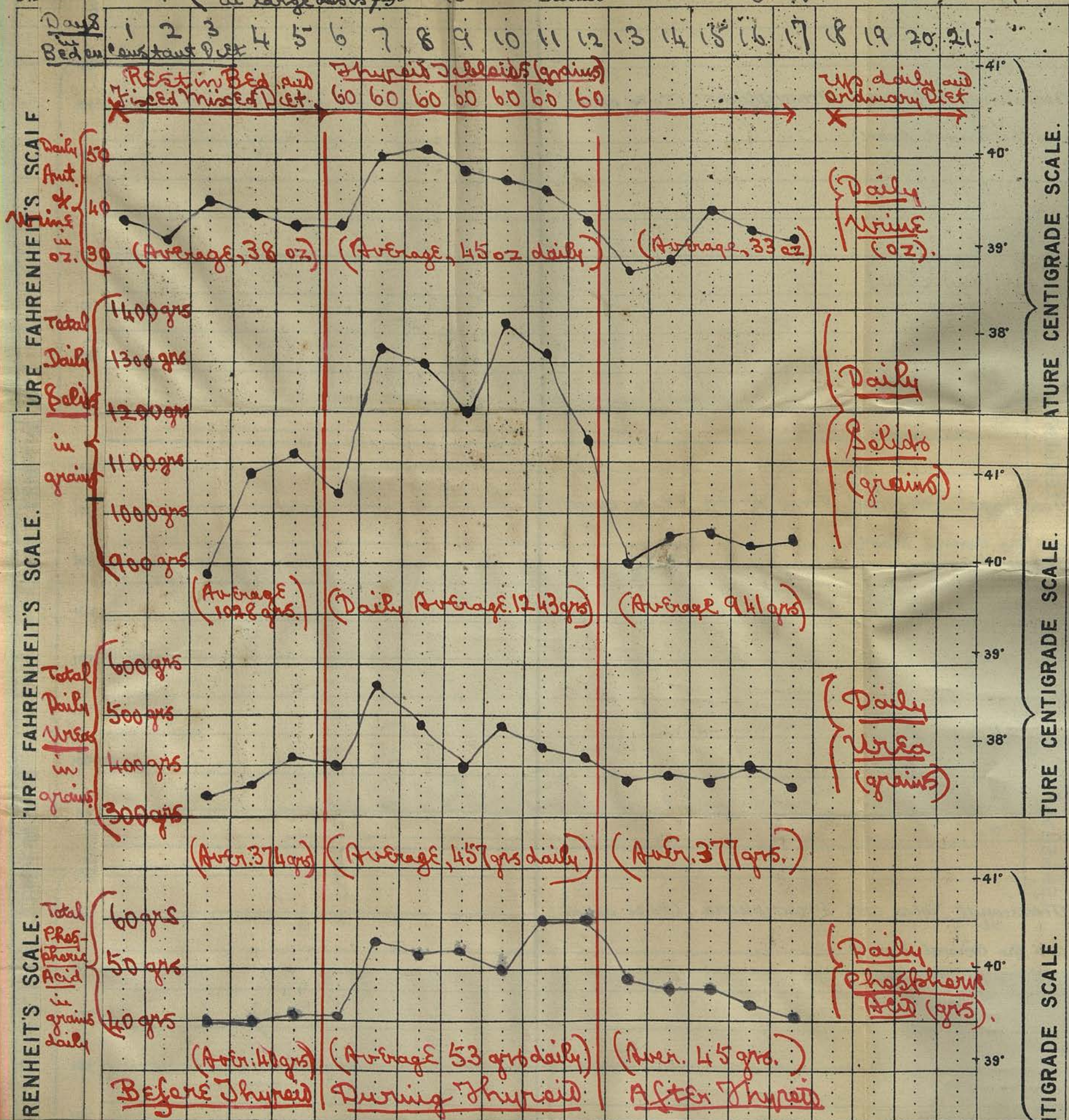


Complications

Occasional Notes an  
into the General Report

Thyroid Chart  
No. II.







From the preceding Table (D.R.) it will be seen that during the 7 days of the drug there was an average daily increase of 7 oz. urine, of 215 grs. total solids, of 33 grs. urea, and of 13 grs. phosphoric acid. On the accompanying chart (page) these results are seen more graphically.

TABLE II) G.W. Aet. 17. ADOLESCENT MANIA.

Day in Bed or Fixed Diet.	Amount of Urine (oz.)	Specific Gravity	Total Solids (grains)	Total Urea (grs.)	Total Phosphoric Acid (grs.)
1 "	36	1028	—	—	—
2 "	44	—	—	—	—
3 "	37	1028	1043	345	36
4 "	35	1029	1015	322	37
5 "	48	1026	1248	422	45
6 Myrcid	51	1024	1224	448	50
7 " 60 grs.	72	1025	1800	532	62
8 "	70	1021	1470	490	60
9 "	50	1026	1300	480	60
10 "	50	1027	1350	440	64
11 "	55	1029	1595	577	66
12 " (Stop)	60	1027	1620	606	61
13 Fixed diet	53	1025	1325	535	46
14 " cont.	68	1025	1700	575	65
15 "	70	1025	1750	560	63
16 "	68	1022	1496	545	58
17 "	53	1020	1060	412	49
18 Ordinary Diet begins.	—	—	—	—	—

Daily  
Aver.  
-age  
40 oz.

Av.  
1102

Av.  
363

Av.  
39

Daily  
Aver.  
58  
oz.

Av.  
1480

Av.  
510

Av.  
60

Aver.  
62  
oz.

Av.  
1466

Av.  
525

Av.  
56

The preceding case in which the effect of the drug on the urine was probably intensified by the mania present, shows that during the 7 days of thyroid administration, there was an average daily increase of 18 oz. urine, 578 grs. total solids, 147 grs. urea, and 21 grs. phosphoric acid; and further that this increase was continued for nearly a week after the drug.

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### SUMMARY.

Hence thyroid extract in large doses (equivalent to one sheep's gland given daily for a week) produced in a series of 92 insane patients treated under conditions of rest in bed and a fixed mixed diet, the following typical effects:- A good subfebrile pyrexia, a loss in weight of 6 lbs., flushing of the skin and perspiration with accompanying loss of water and of some carbonic acid and urea, diminution of the subcutaneous fat, a slight anaemia due more particularly to diminution of haemoglobin, distinct sensory motor and mental excitation, an increase of the pulse rate by 30 or 40 beats per minute with subsequent irregularity weakness and softness, distinct diminution of the blood-pressure, an increase of about six respirations per minute, indicating probably an increase of tissue oxidation to the extent of about a fourth of its previous activity, a tendency to temporary anorexia and dyspepsia, and a considerable increase in the water and solids of the urine, amounting in the case of the water to about a fifth of its previous quantity, and in the case of the solids to about a fourth of their original amount, urea being usually increased a fourth and phosphoric acid a third of their <sup>previous</sup> respective quantities.

### II. MODERATE DOSES. (8 Cases)

Thyroid in moderate doses equivalent to half a gland /

gland daily, continued usually for two weeks but in the various cases from one week to one month, produced reactions essentially similar in kind to those obtained with large doses and differing indeed but little in degree in many cases. In fact half a thyroid daily for two weeks produced much the same effect as one gland daily for one week. Two of the cases were myxoedematous and reacted more markedly than the majority of the cases with large doses. Excluding the two myxoedemic cases, I found that the remaining six gave the following results. Pyrexia, absent in two cases, was subfebrile in the others, but was a poorer and more irregular reaction than in the cases with large doses. Loss in weight amounted on the average to 4 lbs. but ~~was~~ not constant, one patient who took 8 grains of thyroid daily for three weeks gaining 2 lbs. Increased perspiration usually occurred, and also an improved condition of the skin afterwards. Diminution of haemoglobin and of red blood corpuscles occurred only in one case out of three examined. Mental excitement in the form of restlessness, talkativeness or hysterical giggling were common, but the sensory motor and trophic functions were usually unaffected. The pulse was increased by 15 to 20 beats per minute but was not specially weakened. Respirations were usually increased by 3 per min. Anorexia and nausea occurred in <sup>half</sup> ~~1~~ of the cases. The total solids/



solids, urea, phosphates, and urates were increased in the urine but not so markedly as in the case of the large doses.

### III. SMALL DOSES. (15 Cases).

Thyroid in small doses equivalent to from  $1/4$  to  $1/6$  to  $1/12$  of a gland per diem, continued for from 3 weeks to three months, produced similar but less striking and less constant effects as a rule. One of the patients was the cretinoid idiot of 21 years already referred to. She was given one tabloid ( $=1/12$  of a gland) daily for a month; during the first week she exhibited a poor subfebrile pyrexia and mental excitement in the form of screaming, biting and spitting - features she had not previously displayed; during the fourth week she menstruated for the first time in her life, and it was found that she had lost 14 lbs. in the month. After this she was given half a tabloid a day for the following two months, but she exhibited no further reactions nor I may add, any mental improvement. Excluding this cretinoid case I found the following to be the chief features in the other 14 cases. Pyrexia, absent in nearly half of the cases, was subfebrile in the others, and in some of these was a good reaction. Loss in weight when it occurred amounted on the average to 6 lbs., but being spread over periods of several weeks, it was gradual and not so striking as /



as the similar rapid loss in one week with large doses. One stout female lost 12 lbs in 3 weeks. Three Patients on the contrary gained weight with the small tonic doses of thyroid. Perspiration was occasionally increased. Nervous symptoms were not noticeable, and mental excitement in mild form occurred in only three cases. The pulse was usually increased by from 6 to 10 beats per minute, and the respirations by from 1 to 3. No obvious changes were produced in the alimentary functions, but three of the patients had carcinoma affecting the lower lip, the oesophagus, and the pylorus respectively, and in the pyloric case there was undoubted temporary benefit from the use of the drug. The urinary solids urea and phosphates were slightly increased, and in two patients slight temporary albuminuria occurred.

#### IV COMMENCING SMALL DOSES GRADUALLY INCREASED TO MODERATE AND FINALLY TO LARGE DOSES.

administered in the course of from 3 to 4 weeks, were tried in 5 cases. Here the reactions were similar in kind, but gradually became more accentuated as the drug was increased. Thus a pyrexia which was at first poorly subfebrile, became a good subfebrile one; the weight decreased more rapidly, the pulse and respirations became perceptibly quicker with each increment of the dose; and mental excitement became more in evidence./

idence.

Finally it remains to be said that the 120 cases upon which the preceding observations have been based, included the cases of several patients in whom, on account of a distinct mental improvement having followed the first trial of the drug, thyroid was administered on more than one occasion. Thus one patient had the drug no less than five times; another patient had thyroid four times, three patients had it three times; and seventeen patients had the drug twice. It will thus be seen that there were 120 separate cases of administration of the drug amongst 90 different patients. The object of course in repeating the drug in any particular case was to see whether the improvement on the former occasion would not go on to recovery on the next. In many of these cases the same dose was given on each occasion, but in a considerable proportion the dose was varied on one or more of the subsequent occasions. These cases brought out the interesting fact that a patient's susceptibility and mode of reaction to the drug seemed to vary at different times, even when the same doses were used. Thus one stuporose female patient had the drug in large doses on three occasions, with an interval of six months between each administration. On the first occasion the drug had to be stopped on the fourth day owing to thyroid dyspepsia; on/

on the second occasion the drug was borne well and was not stopped until the 7th day when the thyroid fever had just ceased; and on the third occasion the drug had to be stopped on the 4th day owing to the state of the thyroid pulse. Such a variation in the reactivity of the same patient to the drug may help to explain the obscure fact of thyroid idiosyncrasy, and at the same time it indicates the impossibility of predicting with precision how the drug will react in any given individual. As regards the toleration of the drug, while each patient reacted more or less according to his or her own idiosyncrasy, as a rule small and moderate doses were well borne, but as was to be expected the cretinoid idiot reacted strongly to small doses, and the two myxo<sup>ε</sup>edemic patients similarly to moderate doses. In the case of large doses, thyroid was borne badly by those below 20 and especially by those above 60, the former showing a tendency to lose much weight, and the latter exhibiting a special tendency to heart-failure. Thyroid in large doses was also badly borne by patients who were previously emaciated or tending to lose weight, but it was borne worst of all by obese patients and especially where fatty degeneration of the heart was present. In all these cases therefore the drug is physiologically contra-indicated/

contra-indicated, and if therapeutically advised it should be given with caution and <sup>only</sup> preferably in small or moderate doses.

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CONCLUSIONS AS TO THE PHARMACOLOGY OF  
THYROID EXTRACT IN THE INSANE.

The preceding facts show undubitably that thyroid extract in the insane acts as a profound metabolic, that is katabolic stimulant, for in man as in all animals, metabolism is characterised by its katabolic phase, or the splitting up and oxidation of the complex tissue substances. The most constant and the most marked and therefore the most typical effects, are obtained when the drug is exhibited, as was done in the great majority of the cases, in full physiological or so-called toxic doses. With the patient at rest in bed and on a fixed mixed diet, a dose equivalent to one gland daily (e.g. a tea-spoonful of dry extract) given for a week, causes a great increase in the excretion of all the main products of metabolism, especially in the water and carbonic acid and to a less extent in the urea and other nitrogenous products, accompanied by a loss in weight at the rate of nearly one lb. a day and also usually by some degree of pyrexia. The increased elimination of the excreta is effected mainly by the kidneys and the lungs, also distinctly by the skin, but to no appreciable extent by the bowel. If one may assume that under the conditions of rest and diet, the majority of my patients eliminated/

eliminated daily before the drug on an average 40 oz. of water and 1000 grains of solids by the urine (these were the approximate figures in most of my cases and they correspond to those in health), and on an average 8 oz. of water and 8 oz. of carbonic acid by the lungs (these are the estimations under ordinary conditions in health), and further if during the drug, as occurred in the majority of my cases, there was an average daily increase of the urine by a fifth, of the urinary solids by a fourth, and of the respiration by a fourth to a third, then one may say that the average daily loss of nearly 1 lb. in weight was approximately made up as follows:—about  $\frac{1}{2}$  an oz. of organic and inorganic solids, by the urine mainly; about 2 oz. of carbonic acid gas by the breath mainly; and about 12 or more oz. of water, by the urine sweat and breath. This of course is a rough calculation but it gives a fair idea of the effect of thyroid extract in large doses on the extent and mode of elimination of the additional excretory products. According to our modern conceptions of ultimate cell metabolism, the bioplasm (organized proteid) or only living constituent of the cell dominates the changes in the other organic constituents, namely in the unorganised proteid which forms the immediate source of nourishment of the bioplasm itself, and in the carbohydrate and fat which form the immediate source of the energy of the cell, the/

the inorganic salts and water of the cell being largely unchanged and seeming mainly to play the subsidiary rôle of providing a suitable medium in which the preceding vital changes may take place. We must therefore conceive of thyroid as a powerful stimulant of the bioplasm of cells, inducing in it and in the other organic contents these katabolic changes characteristic of metabolism in man. Now it is customary to speak of nitrogenous and non-nitrogenous metabolism as if they were processes which occurred apart from one another in cells, but to my mind this cannot be so if we are to regard the bioplasm as dominating the metabolism of the cell and as being at the same time itself metabolised in the process, that is, split up and oxidised. All the organic constituents - proteids, organized and unorganized, carbohydrates and fats - are being concomitantly metabolised, but at the same time they are metabolisable in different degrees. Fat is probably the most easily metabolised, for according to Foster, it is the most fluctuating of the tissue substances, being the most readily formed and the most easily lost of the body-stuffs. Proteid is probably the most stable of the tissue-substances, for according to Voit tissue proteid is metabolised daily in health only to the extent of about 1 per cent of its substance. Hence I take it, it holds good that whenever a metabolic stimulant/



stimulant is introduced in sufficient quantity into the system, the fats will suffer relatively most at first, and the proteids will suffer relatively most at last. This certainly seems to be the case during thyroid feeding. The fats of the tissues suffer most severely, the diminution of subcutaneous fat being obvious, and probably amongst the fats thus affected are to be included the phosphorised constituents of the central nervous grey matter. The early increase of water in the urine and sweat and the early appearance of the pyrexia point more particularly to the relatively greater combustion of fat during the earlier stage of the drug. The tissue carbohydrates are probably also considerably oxidised, and although the clinical proof of this is ~~is~~ not so clear, the muscular weakness and incapacity for physical exertion during thyroidism may indicate that the glycogen in the muscles, which is the chief immediate source of muscular energy, has been largely burnt up and so is not available. The tissue, proteids are also excessively wasted, and relatively more so in the later stage of the drug, as shown by the tendency in many cases for the <sup>a</sup>ozoturia to continue for some time after the drug has been stopped, the water of the urine during this time falling to its previous level or often lower for a few days. Of the tissue-proteids involved, probably the unorganized proteid is affected, but the feeling of great exhaustion/

tion which occurs when the drug has been much pushed, may possibly indicate that the living proteid itself has been unduly katabolised in these cases, as it probably is to some extent in all cases.

After the active principle of thyroid extract is eliminated from the system, the appetite increases, fat is laid on, and a gain in weight sets in, which is often remarkable. The rationale of this powerful anabolic reaction seems to me to be explainable by Hering's Theory of the "Internal Self-adjustment of Bioplasm,"\* according to which the bioplasm, when it is being katabolised by some stimulant, as for example thyroid, tends more and more to resist the katabolic change and more and more to undergo the reverse change of anabolism, which therefore sets in with a rebound as soon as the katabolic stimulus is removed by elimination.

During thyroid feeding the active principle of the drug is undoubtedly distributed by the blood to the tissues generally, whose metabolism is probably stimulated in the way above described. Is there any evidence to show that the active principle of thyroid preferentially selects the bioplasm of the central nervous system, thus acting as a specific stimulant of the metabolism of the nerve centres, and so intensifying along nervous lines the metabolism of the peripheral tissues which is already being increased from the/

\* Schüüer's Phys. Vol. I. p. 870.  
~~cf. ibid. p. 945~~

\* X

the blood side. Cyon has shown that the excitability of the sympathetic nerves of the thyroid is increased by thyroid administration. In exophthalmic goitre the tachycardia may similarly be due to stimulation of the acceleratory sympathetic centre in the medulla oblongata by excessive or perverted thyroid secretion. The acceleration of the pulse in thyroidism is in my opinion probably due to a similar stimulation of the same nerve centre. It is the earliest symptom of reaction to the drug, and its early disappearance during thyroid feeding, and the early occurrence of sensory, motor and mental excitations - even in the absence of pyrexia - and the concomitant increase of phosphoric acid in the urine, all seem to me to indicate that thyroid specifically stimulates the metabolism of the cerebral nerve centres. In support of this view I may mention that I fed two healthy rats (each weighing  $6\frac{1}{2}$  oz.) upon porridge and water, but to one of them was also given daily one powdered thyroid tabloid. The thyroidised rat <sup>died</sup> with tremors and other nervous symptoms on the fourth day. The healthy rat was killed instantaneously the same day. The brains were hardened in corrosive sublimate, cut by both the freezing and the paraffin methods, and stained variously with toluidin-blue, thionin (Lugaro's method), and methyl-violet (Ford Robertson's method), this work being carried out in the/

X Schüger. op. cit. p. 945.

the Conjoint Laboratory of the Scottish Asylums. While the brain-cells of the healthy rat were normal in appearance, those of the thyroidised rat showed distinct and advanced chromatolysis, many of them being "ghost-like" and indicating that their bioplasm had been katabolised to death.

The facts of thyroid feeding in the insane distinctly favour the "internal secretion" theory of the gland's action, and indicate beyond doubt that thyroid supplies iodothyron and possibly other active principles which are essential to the healthy metabolism of the tissues in general, and probably above all to the nutrition of the nerve-centres. What is the significance of the early development of the thyroid in the embryo, and of its relatively large size in the foetus? May it not have a distinct relationship to the intra-uterine nutrition of the brain which, as is well known, is relatively to the body larger at birth than at any time during life? May not the rapid relative <sup>rise</sup> ~~disease~~ of the thyroid during the first month of extra-uterine life not indicate that brain metabolism is now less dependent upon thyroid secretion, taking instead as its stimulus the constant stream of afferent impulses which come by way of the eyes and ears and kin.

\*  
Berry Hart has recently drawn attention to the direct relationship which subsists in the foetus between the different /

different degrees of development of the connective tissues on the one hand and the relative accessibility of thyroid secretion to them on the other hand. Myx-<sup>\*2</sup> edematous women have in two rare cases (Cawady & Ord) been noticed to improve during pregnancy, probably from absorption of foetal thyroid secretion. Why is the thyroid larger in women than in men, and why does it enlarge at menstruation and pregnancy? I am not aware that any rational explanation of these facts has been offered, but would suggest that they indicate a provision by Dame Nature to supply to the maternal blood an extra supply of thyroid secretion, for the promotion in its earliest stages of the growth and nutrition of the central nervous system of the embryo which as we know is the first system to be laid down in the embryo, and takes the lead of the others throughout foetal development. *Or it may mean an*

*increased demand upon the thyroid by the increased metabolism of the uterus and mammary glands.*

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\*<sup>1</sup> Berry Hart. Scott Med. & Surg. Journ. March 1900.

\*<sup>2</sup> Berry Hart op. cit. (see page ).

D. THERAPEUTIC USES OF THYROID EXTRACTIN THE INSANE.

The following is a Summary of the cases of the 90 different patients whom I have treated for their insanity with thyroid extract. For the sake of clearness, and also in keeping with the nomenclature of other diseases, I use the terms acute, subacute, and chronic, in reference to the duration of the insanity, and the terms simple or mild, moderate, and severe, in relation to the intensity of the disease. Other descriptive terms <sup>ap</sup> of ~~of~~ pertaining more particularly to "mental diseases" or "the insanities" as some prefer to call them, are employed in the same sense as by the recognised authorities on the subject. For the sake of convenience and in accordance with the clinical histories of the patients, but without any pretensions to a classification of mental diseases, I have arranged the cases primarily into three main groups - (1) These incidental more particularly to the period of growth and development, embracing the congenital, pubescent, and adolescent cases treated. (2) Those incidental more particularly to the period of/

of adult life or maturity, embracing gestational, puerperal, and lactational cases; myxoedematous, phthisical, influenzic, and alcoholic cases; cases of general paralysis; and idiopathic cases from mental worry or shock and bodily wear and tear. (3)  
Those incidental more particularly to the period of decadence, embracing climacteric and senile cases.

### I. CONGENITAL CASES.

1. (M.F.). Cretinoid Idiot. Female. 21 years.  
Father and brother insane and mother intemperate.  
Patient sent to asylum as not properly looked after at home and unable to look after herself. During first 9 months becomes stouter and distinctly cretinoid looking. Thyroid not palpable. Seen by Dr. W.W. Ireland who confirmed diagnosis as to cretinoid features. Given thyroid extract in small doses for 3 months; mentally excited during first week of drug, menstruated on 26th day for first time in her life, lost 14 lbs. in weight in the first month; showed no further change in body or in mind during second and third months. Drug therefore stopped. Result unimproved. Still in asylum.

2. (C.R.). Congenital Imbecile (mild). Female 32 years. Brother and paternal uncle insane. Has had/



had several attacks of simple mania since adolescence. Sent to asylum on account of another maniacal attack, which however subsided shortly after admission. Given thyroid in large doses empirically, to observe effect on the imbecility.

Result Unimproved. For two weeks after the drug she was somewhat more sensible and more settled in conduct (probably as the result of extra attention and discipline), but after this was as before. Has since been spending her time between home and asylum.

3.(I.G.) Congenital Imbecile (mild) with epilepsy (petit mal).

F. 36 years. History unknown. Sent to asylum on account of mild epileptic mania, which soon passed off. Given thyroid in large doses empirically, to observe effect on imbecility and on epilepsy. Result -Unimproved. Sent to poorhouse.

II. PUBESCENT CASES.

4. (G.W.) Male. 17 years. A backward boy. Originally at 15 Pubescent Mania of acute severe type, with subsequent deterioration and tendency to relapses of mania of the same type. Given thyroid in large doses/

doses at 17 during a quiescent period, being then  $1\frac{3}{4}$  years ill. (8 mos. in asylum). Reacted strongly to the drug losing 25 lbs. in weight and temporarily more excited and confused mentally. Result - Unimproved. Still in asylum, becoming demented.

5. (J.M.) F. 17. Maternal grandparents insane. Originally with onset of menstruation at 16, Pubescent Mania of mild type, with subsequent deterioration. Given thyroid in large doses at 17, being 14 months ill (12 in asylum). Result - Unimproved. Is now fat and mildly demented but able to be at home..

### III. ADOLESCENT CASES.

6. (I.N.). 19 F. Maternal uncle and paternal uncle insane, and paternal grandfather epileptic. Originally at 19 Adolescent Melancholic Stupor remains stuporose and resistive, making no progress: given thyroid in large doses, being 4 months ill (3 in asylum): reacted strongly, losing 12 lbs: Result - Unimproved. This patient subsequently had a sharp attack of influenza (temp. 104 F) which threw her back for a time mentally, was afterwards treated with ovarian and with cerebral extracts, passed into a state of simple mania, and finally recovered, after

20 months illness.

7. (A.M.L.) 28 F. Brother insane. A romp as a girl but became melancholy and reserved as she grew up. Originally at 28 Adolescent Melancholic Stupor, with masturbational tendency: makes no progress: given thyroid in large doses, being ill 8 months. (2 mos. in asylum). Reacted well, losing 12 lbs. but ultimately gaining 20 lbs. Improved but still dull and stupid. Six months later sent home.

8. (M.O.) 29 F. Father insane. Patient naturally hypochondriacal. Originally at 28 Adolescent Mania, at first acute and severe in type, then subacute and mild, with incipient dementia. Given thyroid in large doses at 29, being ill 8 months (6 mos. in asylum). Result - Improved temporarily. Tried at home. Gradual deterioration and dementia. Sent back to asylum, and given thyroid in large doses again at 31, being ill 3 years. Result - Improved, and able to be taken home again but needs constant attention.

9. (W.R.) 24. M. Maternal aunt insane. At 24 Adolescent/

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Adolescent Melancholic Stupor, with masturbational tendency: remains mildly stuporose and apathetic: given thyroid in large doses at 24, being ill 9 months (6 mos. in asylum). Result - Recovered.

10. (E.M.). 28. F. Had a previous attack of melancholia at 23. At 27 Adolescent Melancholic Stupor, with incipient dementia. Given thyroid in large doses at 28, being ill 9 months. (8 mos. in asylum): Reacted well. Improved temporarily. Finally demented and sent to country.

11. (C.R.) 20. M. "Relatives" insane. At 19 Adolescent Mania of simple type, with masturbational tendency and incipient Dementia. Given thyroid in large doses at 20, being ill 20 months (18 mos. in asylums). Unimproved. Finally mildly demented, and sent to country.

12. (J.P.) 28. F. Paternal grandfather and two paternal aunts insane. At 26 Adolescent Melancholia, with hypochondriacal and hysterical features: makes no progress. Given thyroid in large doses at 28, being ill 2 years. (6 mos. in asylum). Unimproved. Finally mildly demented, and sent home.

Chronic/

Chronic cases of the Adolescent group, that is, patients whose insanity was originally adolescent, but at the time of thyroid treatment was of over two years' duration and had assumed distinctly chronic features.

13. (M.S.). 26. F. Maternal uncle insane. Previous attack at 18. At 24 Adolescent Mania of mild type, followed by gradual deterioration and dementia.

An adolescent degenerate. Thyroid in small doses at 26, being 26 months ill (24 mos. in asylum).

Unimproved. Finally demented, and sent to poorhouse.

14. (E.S.). 23. F. Previous attack at 18. At 21 Adolescent Mania of mild type, followed by mild secondary stupor and dementia. Thyroid in large doses at 23, being  $2\frac{1}{4}$  years ill in asylum. Unimproved. Still in asylum.

15. (M.R.C.). 20. F. Parents neurotic. P.A. at 16. At 18 Adolescent Melancholic Stupor, with tendency to alternate with Mania: probably incipient "Folie circulaire". Given thyroid in large doses first at 20, being then  $2\frac{1}{4}$  years ill in asylum, maniacal at the time, and improved; again at 22 (3 years ill) to/

to cut short an attack of mania, and improved; and again at 23 ( $4\frac{1}{2}$  yrs. ill), to abort an imminent relapse of mania. Relapse aborted. Still in asylum.

16. (I.L.). 26. F. Mother and paternal cousin insane. P.A. at 17. At 23 Adolescent Mania of acute severe type, followed by secondary stupor and mild dementia. Given thyroid in large doses at 26, being 3 years ill in asylum. Improved temporarily. Sent to poorhouse.

17. (L.E.). 24. F. Maternal grandmother insane. At 21 Adolescent Melancholic Stupor followed by mania and finally by mild dementia. Given thyroid in large doses at 24, being  $3\frac{1}{4}$  years ill (3 yrs. in asylum). Unimproved. Sent to poorhouse.

18. (E.M.Z.). 25. F. Father insane. Patient an adolescent deteriorate and prostitute. At 20 Adolescent Mania of acute severe type, with tendency to similar relapses for 3 years, and then secondary stupor and dementia. Given thyroid in large doses at 25, having been  $5\frac{1}{2}$  years ill in asylums. Unimproved/

Unimproved. Died fully 1 year later from acute pulmonary phthisis.

19. (H.B.G.P.). 31. F. Brother and cousins insane. At 25 Adolescent Mania, at first acute and severe in in type, gradually subsided and ended in mild dementia. Given thyroid in large doses at 31, having been  $5\frac{3}{4}$  yrs. ill in asylums. Unimproved. Still in asylum, stout and demented.

20. (Mrs. M.M.C.). 32.F. Two maternal uncles and one maternal cousin insane. Excitable unstable adolescent, "fast" in habits. At 24 Adolescent Mania, of acute severe type, with homicidal and suicidal tendencies: gradually becomes distinctly recurrent, the maniacal attacks maintaining the same general character but coming to exhibit such extraordinary explosiveness as almost to suggest Mental Epilepsy. During the remissions is well enough to go home. The problem of Morningside for years. Given thyroid in large doses at 32, being ill 8 years. Unimproved. Died a year later from acute pneumonia.

#### IV. INSANITIES OF CHILD-BEARING.



21. (Mrs. J.C.D.). 21. F. At 21 Puerperal Mania, acute and severe, followed by mild secondary stupor: makes no progress: given thyroid in large doses at 21, having been ill 4 months in asylum: reacted well. Recovered, - and has since had another baby without any ill effects.

22. (Mrs. M.N.H.). 30. F. At 30 Puerperal Mania of moderate type - delusional taciturn and resistive: makes no progress: given thyroid in large doses at 30 - being 4 months ill (3 mos. in asylum). Improved, but remains suspicious and taciturn till 9th month of illness, when menstruation returned for the first time and coincidently with this recovery set in and was complete.

23. (Mrs. J.W.A.) 39. F. Two paternal uncles insane. P.A. of puerperal mania at 23 and of lactational mania at 25. At 39 Puerperal Mania of moderate type, followed by mild stupor; makes no progress. Given thyroid in large doses at 39, being 4 months ill (3 mos. in asylum). Reacted strongly. Improved temporarily, tried at home - but relapsed. Now chronic, and in asylum.

24./

24. (Mrs. E.F.D.). 30. F. At 30 Puerperal Mania, at first acute and severe in type, gradually subsides: remains delusional and confused: tried with mammary gland extract at 3½ months but unimproved. Given thyroid in large doses at 30, being 5½ months ill in asylum: reacted well. Made an excellent recovery.

25. (Mrs. A.M.M.). 29. F. "Uncle" insane. At 29 Lactational Melancholia of mild type; makes no progress. Given thyroid in large doses at 29, being ill 6 months (4 mos. in asylum). Reacted well. Recovered.

26. (Mrs. J.B.L.S.). 24. F. Neurotic family. At 24 Puerperal Melancholia of mild or simple type; makes no progress: given thyroid in large doses at 24, being 6 months ill (4 mos. in asylum). Poor reaction. Unimproved. Finally taken home where she remained more or less dull and apathetic.

27. (Mrs. M.J.C.). 37. F. At 37 Puerperal Melancholia, with delusions confusion and excitement: makes no progress: given thyroid in large doses at 37, ill 6 months (4 mos. in asylum): reacted strongly. Unimproved. Now chronic and in asylum.

28. (Mrs. H.F.D.). 29.F. At 29 Lactational Melancholia/

Melancholia with suicidal tendency: becomes delusion-  
al and stuporose: given thyroid in large doses at  
29, being 6 months ill (5 mos. in asylum), and  
improved temporarily; then becomes maniacal at 30,  
with incipient dementia. Given ovary and brain  
extracts, and thyroid again at 31 in moderate doses,  
being  $2\frac{1}{2}$  years ill. Unimproved. Now chronic and  
in asylum.

29. (Mrs. M.S.G.) 37. F. Brother insane. At 37  
Lactational Melancholia with delusions of suspicion,  
gradually becomes an angry scolding maniac. Given  
thyroid in large doses thrice at 37 (1 yr. ill,) 38 & 39: Improved temporarily on first and second  
occasions, unimproved on third. Now chronic, and  
in asylum.

30. (Mrs. M.S.K.) 28. F. P.A. at 25. At 27  
Puerperal Melancholia with delusions of suspicion,  
and incipient dementia. Thyroid in large doses  
twice at 28, being ill 13 and 17 months in the  
asylum on the two occasions. Improved temporarily  
on both occasions. Finally demented and sent to  
country.

31. (G.S.R.) 26. F. Single. P.A. at 21 of puer-  
peral/

peral mania. At 24 Puerperal Mania of simple variety, then in 6 months secondary stupor and apparently incipient dementia. Given thyroid in large doses at 26, having been ill 2½ years in the asylum. Made a remarkable recovery.

Chronic cases of this group, that is, patients whose insanity originated in connection with child-bearing, but did not come under thyroid treatment until chronicity was established.

32. (Mrs. M.H.D.) 30. F. At 27 Simple Melancholia of pregnancy, becoming chronic: patient came voluntarily to asylum in order to have Thyroid treatment: given thyroid in large doses at 30, being 2 years ill, Improved temporarily, but finally as before. Still melancholic, but at home.

33. (Mrs. M.B.S.). 36. F. At 32 Puerperal Melancholia with delusions, became chronically delusional and maniacal: given thyroid in large doses at 36, being ill 3 years (mostly in asylum). Unimproved. Still in asylum.

34. (Mrs. J.R.). 30. F. Brother, sister and cousin insane. At 26 Lactational Melancholia with suicidal tendency/

tendency, passed into stupor, and finally on to dementia. Given thyroid in large doses twice at 30 (4½ years ill in asylum), unimproved, but became maniacal with tendency to insane decoration for five months; and at 31 (5 years ill), Unimproved. Sent to poorhouse.

35. (Mrs. M.M.L.). 33. F. "Family" insane. At 26 Lactational Mania of acute severe type, with secondary stupor and dementia. Thyroid in large doses at 33, being 7 years ill in asylum. Unimproved. Sent to country.

36. (Mrs. E.F.S.). 50. F. Sister and paternal aunt insane. Several P.As., from 20th year onwards. At 31 became permanently insane during her last pregnancy and confinement. Mania of severe type, becoming distinctly recurrent. Ill for 20 years in asylum. Thyroid given in large doses on 4 occasions to cut short threatened attacks of the mania: thyroid succeeded in aborting the mania on 1st, 2nd, & 4th occasion, but not on 3rd, on which the mania was established before the drug was begun. The patient was thus improved on three out of the four occasions on/

on which the drug was used.

V. INSANITIES OF MYXOEDEMA.

37. (Mrs. A.S.M.M.) 37. F. Family neurotic. At 37 Myxoedematous Melancholia, with delusional and suicidal tendencies, gradually becomes worse, the myxoedema which was only suspected at first becoming more evident. Given thyroid in moderate cases at 37, having been 11 months ill (7 mos. in asylum). Marked reaction. Myxoedema disappeared and mental recovery set in, and thyroid in small doses being continued, recovery was permanent.

38. (Mrs. M.A.M.L.) 38. F. Myxoedema since 33 but not diagnosed till 38. At 38 Myxoedematous Melancholic Stupor, with delusional and resistive tendencies. Thyroid in small doses at 38, having been myxoedemic for 5 years, and insane for a month. Slight temporary improvement: 3 months later thyroid in moderate doses, improved distinctly but relapsed: thyroid in large doses at 9th month of insanity, with improvement as before, followed by small doses to maintain improvement but fails and although small small doses are continued for 3 months, becomes mentally/



mentally worse, more delusional and more resistive. At 39 thyroid again in large doses, but only slight temporary improvement mentally. After each dosing of thyroid reacted well and desquamated freely, and myxoedema disappeared but insanity remained. Patient died at 40 of phthisis pulmonalis.

#### VI. GENERAL PARALYSIS.

39. (Mrs.M.B.). 51.F. Had 3 miscarriages. (Syphilis denied). At 50 General Paralysis, with much Simple Exaltation. Given thyroid in large doses at 50, being 9 months ill (6 mos. in asylum). Reacted well. Unimproved. Died at 53.

40. (Mrs.C.F.G.). 35.F. History unknown, but led the life of a hawker. At 34 General Paralysis, with much stupor and resistiveness. Given thyroid in large doses at 35, being 15 mos. ill (1 year in Asylum) Reacted strongly and lost 17 lbs. Unimproved. Died 6 mos. later.

#### VII. ALCOHOLIC AND MORPHIA CASES.

41. (Mrs.C.D.M.). 29.F. At 29 Alcoholic Melancholia. Suicidal, delusional, and stuporose. Makes no progress./

gress. Given thyroid in large doses twice at 4th and 8th month of illness in asylum: improved both times: finally mildly demented but able to stay at home.

42. (M.A.C.). 33 F. At 33 Alcoholic Melancholic Stupor, remains stuporose and delusional: given thyroid in large doses at 33, being 5 mos. ill in asylum: unimproved, but becomes manical<sup>a</sup> (simple mania) for a month after the drug. Given thyroid again at 33, but in moderate doses, now being 8 mos. ill; again became manical<sup>a</sup>. Finally a chronic delusional maniac<sup>al</sup> case; sent to poorhouse.

43. (D.R.) 43 M.P.A. of alcoholic insanity at 40. At 42 Alcoholic Melancholia Stupor, makes no progress: Stupor with incipient dementia. Given thyroid in large doses at 43, being 13 mos. ill (11 mos. in asylum). Improved temporarily. Dement, still in asylum.

44. (E.D.). 38 F. Father brother and sister insane. Patient neurotic. Prescribed morphia at 25 for a "floating kidney." Morphia habit acquired at 27, and alcoholic at 30, and insane at 37. Mania with delusion/

delusional, erotic, homicidal and suicidal tendencies. Given thyroid in large doses at 38, being 12 mos. insane (7 mos. in Asylum); improved temporarily. Finally chronic and in asylum.

45. (A.K.) 58.M. Intemperate. Many short P.As. of alcoholic insanity from 30 year upwards. At 37 Alcoholic Melancholia with suicidal and delusional tendencies gradually becomes a case of Monomania of Suspicion, and at 58 develops carcinomatous structure of oesophagus. Given thyroid in small doses for 3 mos. at 58, to observe its influence on the carcinoma and the monomania (21 years ill). No effect produced on either. Unimproved. Died 4 months later.

#### VIII. POST-INFLUENZIC INSANITY.

46. (M.A.L.). 30.F. At 30 Post Influenzic Melancholia with incipient dementia. Giving thyroid in large doses at 30, being 6 mos. ill (3 mos. in Asylum): Unimproved. Died a year later from chronic enteritis.

47. (H.M.); 25.F. Brother still insane. At 24 post-influenzic melancholic stupor, with catalepsy and incipient dementia. Given thyroid in large doses at 25/

25, being 1½ year ill (3 mos. in asylum.). Improved temporarily. Demented and still in asylum.

IX. "PHTHISICAL" (TUBERCULAR) INSANITY.

48. (M.C.) 33. F. At 29 "PHTHISICAL." Mania of delusional type; thin and anaemic and tubercular but ~~not~~ phthisical. Suspicious, irritable and asocial. Given thyroid in large doses at 33, being 3 3/4 ill (6 mos. in Asylum. Unimproved. Chronic delusional mania, and still in Asylum.

X. IDIOPATHIC INSANITY.

49 (A.T.P.) 30.M. Father insane. At 30 Idiopathic Melancholic Stupor (from business worry and over work): makes no progress. Given thyroid in large doses at 30, being 4 mos. ill (2 mos. in asylum): unimproved. Finally improves slowly, and fully a year later is tried at home and remains, there.

50. (Mrs.E.H.B). 37.F. At 37 Idiopathic mania of moderate type (from want and adverse circumstances), with incipient Dementia. Given thyroid in large doses at 37, being 6 months ill in asylum; improved temporarily. Since demented, and sent to country.

51 (A.M.) 33 F. At 38 Idiopathic mania of moderate intensity/

intensity (from domestic worry and over-work), followed by mild stupor with delusions, taciturnity, and resistiveness: makes no progress. Given thyroid in large doses, at 33, having been 8 months ill in Asylum. Marked reaction. Loses 10 lbs, but afterwards gains 24 lbs. Makes an excellent recovery.

52. (E.H.) 29. F. Father intemperate, Mother and brother insane. At 23 Idiopathic Melancholia of simple type (from shame and worry over an illegitimate child): makes no progress. Given thyroid in large doses at 29, being 10 months ill (5 mos. in asylum: reacted well: recovered).

53. (I.H.). 29. F. Paternal Aunt Insane. At 28 Idiopathic Melancholia of severe excited type (from "shock at death of lover"): makes no progress. Given thyroid in large doses at 29, being 10 mos. ill (3 mos. in asylum). Unimproved; excitement increased. Died a year later from acute miliary tuberculosis.

54. (J.C.S.). 29.F. at 28, Idiopathic Melancholia with delusional and suicidal features (from a "disappointment in ment in love"): makes no progress. Given thyroid in small doses at 29, being 19 months ill (5 months in asylum/

asylum) Unimproved. Still in asylum.

55 (Mrs.M.N.) 40 F. P.A. at 30. At 39 Idiopathic *Mania* of acute and severe type (from the wear and tear and anxiety of nursing her ill boy), tending to <sup>become</sup> recurrent. Given thyroid in large doses twice a at 40 being ill one year in asylum, and at 41 being 1 $\frac{3}{4}$  years ill. Unimproved. Still in asylum.

56. (Mrs J.A.T.. 55. F. At 5 $\frac{1}{2}$  had a scirrhus cancer <sup>of</sup> ~~at~~ mamma removed by Mr. Chiene and 3 mos. Later from anxiety about her breast she developed Idiopathic Melancholia. Made no progress; treated with ovarian extract extract without benefit. Given thyroid in large doses at 55, being 15 months ill (12 months at asylum.) Reacted markedly, but <sup>un-</sup>improved. This patient 6 months afterwards was tried at home, remained melancholic for for another nine months, and finally after being 2 $\frac{1}{2}$  years ill made an excellent recovery. There has been no recurrence of the melancholia (<sup>new</sup> ~~now~~ three years since) or of the carcinoma (now 5 $\frac{1}{2}$  years since).

57. (Mrs.A.N.W.) 32. F. Sister insane. Patient ~~neurotic~~ neurotic. At 31 Idiopathic mania of acute and severe type (from domestic worry and poverty), passing into Secondary/



Secondary stupor and incipient dementia. Given thyroid in large doses twice, at 32, being 15 mos. ill (6 months in asylum) and at 33 being 20 months ill. Unimproved. Died  $1\frac{1}{2}$  years later (at 35) of acute miliary tubercle of the lungs.

58. (Mrs. E. W. C.) 37. F. At 37 Idiopathic Melancholia with Stuperose and delusional features (from poverty and adverse circumstances). Given thyroid in small doses at 37, being 7 months ill in asylum: improved temporarily. Given thyroid in large doses at 38, being 13 mos. ill in asylum; unimproved. Because demented sent to poorhouse.

59. (E. L.) 33. F. Father insane, Mother "paralysed." At 32 Idiopathic Melancholic Stupor (from exhaustion of nursing her mother); passes through a severe maniacal phase and then into secondary stupor. Given thyroid in small doses at 32, being 9 mos. ill (7 mos. in asylum), but unimproved. Given thyroid in large doses at 33, being 14 mos. ill, but again unimproved. Died  $1\frac{1}{2}$  years latter of tubercular ulceration of the bowels.

60. (Mrs. C. M. M. P.) 32. F. P. A. at 23. At 31 Idiopathic Mania (from domestic worry and overwork), acute/

acute and severe for 4 months, then subacute and moderate for another 12 mos, and then incipient dementia. Given thyroid in large doses at 32, being ill 18 mos. in asylum: unimproved. Mildly demented, but able to return home.

61. (J.B.) 51. M. Brother insane. Several P.As. since 36th year. At 49 Idiopathic Mania of acute severe type (from poverty and adverse circumstances), tending to become recurrent. Given thyroid in large doses at 51, being ill 20 months in asylum and in the Maniacal phase it the time. Unimproved. Still in asylum.

CHRONIC CASES OF THE (ORIGINAL) IDIOPATHIC GROUP.

62. (J.R.). 34.F. Sister insane. P.A. at 20. At 30 Idiopathic Mania of acute severe type (from shock at death of mother), becomes recurrent and chronic. Given thyroid in large doses at 34 during a remission, being ill four years in asylum. Unimproved. Still in asylum.

63. (J.C.C.M.); 40. F. Maternal aunt insane. P.A.s. at 21, 26 and 29. At 33 Idiopathic Mania of acute severe type (from business worry, alternating with Stupor/

Stupor for 2 years: finally stuporose at 35, with incipient dementia. Given at 40 and 41 thyroid in large doses thrice, being ill  $7\frac{1}{4}$  years,  $7\frac{3}{4}$  yrs., and and  $8\frac{1}{4}$  yrs. respectively. Improved temporarily on each occasion. Still in asylum.

64. (J.A.M.) 39.F. At 29 Idiopathic Mania of moderate intensity (from disappointment in marriage), becomes chronic and ends in dementia. A stout dement. Given thyroid in large doses at 39, being 10 years ill in asylum. Stood drug very badly: had only 140 grains of dry extract in 3 days, and lost 11 lbs. Unimproved. Sent later to poorhouse.

65. (T.S.) 61. M. Mother insane. P.A. at 41. At 48 Idiopathic Mania with delusional features, (from shock at death of his wife): becomes a case of Monomania of suspicion and persecution. Also subject to sporadic epilepsy (at 51, 59, 61 and 62). At 61 develops carcinomatous stricture of pylorus. Given thyroid in small doses to observe any influence on the carcinoma and the monomania, being ill two months from cancer and 13 years from insanity. Dyspepsia much benefited, nutrition much improved, and weight increased/

increased. Monomania unimproved. Same treatment repeated at 62, with similar effects. At 64 died from profuse haematemesis. Carcinoma of pylorus found at post-mortem examination.

66. (W.C.) 53. M. History unknown. At 38 Idiopathic Mania, with exalted delusions. Becomes a case of Monomania of grandeur. At 52 epithelioma of lower lip, removed by surgeon. At 53 <sup>ceru</sup>~~clerical~~ glands enlarge. Given thyroid in small doses to observe effect on Carcinoma and monomania. Unimproved. Died.

#### XI. CLIMACTERIC INSANITY.

67. (G.E.C.). 46. F. At 46 Climacteric Melancholia with hypochondrical and suspicious notions: getting worse, refusing food. Given thyroid in large doses at 46, being 4 months ill (3 months in asylum): reacted well, lost 6 lbs. but gained 20 lbs in following 10 weeks and made an excellent recovery.

68. (R.E.W.). 46.F. At 46 Climacteric Melancholia, with delusional, excited and resistive features: gets worse, refusing food daily. Given thyroid in large doses at 46, being 6 months ill in asylum. Unimproved.  
Died

Died  $1\frac{3}{4}$  years later from pulmonary phthisis.

69. (A.R.) 43. F. Paternal grand-parents insane.

Several mild P.As. from 34th year onwards. At 43 Climacteric Melancholia of simple and hypochondriacal type: makes no progress. Given thyroid in large doses at 43, having been seven months ill (5 months in asylum). Recovered.

70. (Mrs. J.D.T.). 51. F. Brother and maternal aunt

insane. At 50 Climacteric Melancholia with suicidal tendency. Given thyroid in small doses at 50, being 8 months ill in asylum. Improved, and able later to go home though still somewhat depressed.

71. (G.B.). 44. F. At 44 Climacteric Melancholia of

visceral <sup>&c</sup> ~~allusional~~ type: excited, resistive, fed regularly with nasal tube. Given thyroid in moderate doses at 44, being 11 months ill (6 months in asylum). Unimproved, more excited. Died 2 months later from exhaustion: at post-mortem, two small uterine fibroids.

72. (E.C.D.). 45. F. At 44 Climacteric Melancholia

of simple type, making no progress. Given thyroid in large doses at 45, being 1 year ill and treated at home by her own request. Improved temporarily, but/

but relapsed, and got worse, and came as a voluntary patient to the asylum where she finally made a good recovery after an illness of  $1\frac{1}{4}$  years.

73. (Mrs.N.P.W.). 54. F. P.As. at 36, 50 and 52. At 53 Climateric Melancholia of simple type: making no progress. Given thyroid in large doses at 54, being 1 year ill in asylum. Improved temporarily, but relapses, remains a chronic mild melancholic<sup>a</sup> and finally sent home.

74. (E.J.P.) 50. F. Father insane. 3 P.As. at 43,44, and 45. At 49 Climacteric Melancholia of simple type, tending to become recurrent. Given thyroid in large doses at 50, being 1 year ill in asylum. Improved temporarily, but relapses and remains a chronic melancholiac.

75. (Mrs.C.S.B.). 47. F. Tubercular and bilious subject. At 46 Climacteric Melancholia with suicidal tendency, and becoming chronic. Given thyroid in large doses twice at 47, being ill 1 year (9 months in asylum) and  $1\frac{1}{4}$  years on the two occasions. Improved temporarily. Becomes a chronic Melancholiac and dies at 49 of pulmonary phthisis.



76. (Mrs. M. R. A.). 46. F. At 45 Climacteric Melancholia, with suicidal, delusional, and excited features, making no progress. Given thyroid in large doses at 46, being 13 months ill (10 mos. in asylum). Unimproved - more excited. Remains a chronic excited melancholiac. Still in asylum.

77. (Mrs. M. G. D.). 49. F. Brother insane. At 48 Climacteric Mania with delusional and excited features. Given thyroid in small doses at 49, being 17 months ill (4 mos. in asylum). Unimproved - more excited. A chronic delusional maniac, still in asylum.

78. (J. McD. D.). 41. F. Paternal aunt and cousin insane. At 40 Climacteric Melancholia, suicidal and excited, with masturbational tendency. Given thyroid in large doses at 41, being 20 months ill in asylum. Unimproved - more excited. Finally sent to another asylum where she dies at 42.

79. (Mrs. E. B. S.). 44. F. Maternal cousin insane. At 43 Climacteric Melancholia of delusional variety passes into delusional mania. Given thyroid in large doses at 44, being 22 months ill (20 mos. in asylum). Unimproved. A chronic delusional maniac. Still in asylum./

asylum.

80. (Mrs. M.W.A.). 47. F. At 45 Climacteric Mania of delusional variety, becoming chronic. Given thyroid in small doses at 47, being 2 years ill ( $1\frac{1}{2}$  yrs. in asylum). Unimproved. Still in asylum.

81. (Mrs. E.H.H.I.). 51. F. P.A. at 22. Tubercular. At 49 Climacteric Melancholia of suicidal tendency, becoming chronic. Given thyroid in large doses twice at 51, being 2 years ill ( $1\frac{1}{2}$  yrs. in asylum) and  $2\frac{1}{4}$  years ill on the two occasions. Unimproved - after each time more actively suicidal. A chronic melancholiac, died at 54 of pulmonary phthisis,

82. (Mrs. M.D.G.). 42. F. At 40 Climacteric Melancholia, suicidal; tending to become chronic. Given thyroid in small doses at 42, being  $2\frac{1}{4}$  years ill (2 yrs. in asylum); unimproved. A chronic melancholiac. Still in asylum.

83. (Mrs. J.D.L.) 46. F. At 43 Climacteric Mania, delusional variety, becoming chronic. Given thyroid in small doses at 46, being  $3\frac{1}{4}$  years ill  
(3/

(3 yrs. in asylum): unimproved. Still in asylum.

84. (H.B.) 48. F. Brother insane. At 45 Climacteric Melancholia, simple variety, becoming chronic and recurrent in type. Given thyroid in large doses at 48 - being 4 years ill (to and fro between home and asylum). Unimproved. A chronic melancholiac becomes suicidal at 50. Still in asylum.

85. (J.M.). 54. F. At 50 Climacteric Melancholia, suicidal; becomes chronic melancholiac with incipient dementia. Given thyroid in small doses at 54, being 4 years ill (3½ yrs. in asylums). Unimproved. Later is sent to country.

86. (Mrs. C.L.A.H. 50. F. At 45 Climacteric Melancholia, delusional and hypochondriacal, becoming chronic. Ill 5 years (only 1 month in asylum) given parathyroid, and then thyroid, in large doses. Improved, - able to return home a month later.

## XII. SENILE CASES.

87. (Mrs. J.B.). 60. F. Intemperate, obese, diabetic P.A. at 54. At 60 Senile and Alcoholic Melancholic Stupor, resistive, glycosuric. Making no progress. Given/

Given thyroid in large doses at 60, being ill at least 3 months. (2 mos. in asylum) Unimproved.

On 7th day of drug signs of heart-failure, followed by mental excitement, exhaustion, and death on 10th day after the drug.

38. (C.C.). 65. F. At 65 Senile Mania, delusional, nasal feeding necessary. Given thyroid in large doses at 65, being 6 months ill in asylum: drug had to be stopped on 4th day owing to state of pulse. Unimproved. Still in asylum.

39. (Mrs. E.P.G.). 61. F. At 60 Senile Melancholia excited, becoming chronic. Given thyroid in large doses at 61, being 12 months ill in asylum. Pulse stood drug badly. Lost 6 lbs. but gained 14 lbs. afterwards, and improved, - excitement subsiding. Remains a chronic simple melancholiac. Died at 64.

\*

90. (Mrs. J.F.S.) 64. F. P.As., at 38 & 52. At 61 Senile Melancholia, hypochondrical and chronic. Given thyroid (at her own request) in approximately large doses at 64, being 3 years ill (2½ yrs. in asylum). Pulse became very irregular; she lost 9 lbs. but gained 21 lbs. in the following 3 months. Unimproved mentally. A chronic melancholiac, but able to return home.

The following table gives a Summary of the results of treatment in the various groups of cases:-

	<u>Recovd.</u>	<u>Imprvd.</u>	<u>Unimprvd.</u>
I. Congenital insanity.	0.	0.	3.
II. Pubescent insanity.	0.	0.	2.
III. Adolescent insanity, and Chronic Insan.	1.	3.	3.
Adol <sup>y</sup> in origin.	0.	2.	6.
IV. Insanities of Child- bearing, & Chron. Insan. simi- lar in origin.	4.	5.	2.
V. Myxoedemic Insanity.	0.	2.	3.
VI. General Paralysis.	1.	1.	0.
VII. Alcoholic &c. Insanity.	0.	0.	2.
VIII. Post-Influenzic Ins.	0.	3.	1.
IX. "Phthisical" Ins.	0.	1.	1.
X. Idiopathic Insanity, and Chron. Ins.	0.	0.	1.
Idiopath. in origin.	2.	2.	9.
XI. Climacteric Insanity.	0.	1.	4.
XII. Senile Insanity.	2.	6.	12.
	0.	1.	3.
	<u>10.</u>	<u>27.</u>	<u>53.</u>

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Hence out of 90 patients treated, 10 recovered, 27 were improved, and 53 were unimproved. As regards the sex of the patients, there were 81 Females, and 9 Males. Of the 81 Females, 9 recovered, 25 were improved, and 47 were unimproved. Of the 9 males 1 recovered, 2 were improved, and 6 were unimproved.

From the above table it will be seen that the best all-round results, the highest proportions of recoveries and improvements, were far and away obtained in the more or less recent forms of the insanities of child-bearing.

The Recoveries naturally form the most interesting group of the results of treatment. Excluding one of the ten recoveries, that of the myxoedematous female, ~~-----~~ who ought to have recovered and did recover, although the other myxoedematous female did not, as regards her insanity, — excluding then the myxoedemic case, I find that there remain 9 recoveries out of 89 cases of insanity treated, that is practically 10 per cent of recoveries, (8 recoveries out of 80 women, indicates a true percentage in women, but 9 cases are too small a number upon which to base any conclusions as to the true rate of recovery in men). Ten per cent of recoveries may not be/



be said to be a very brilliant result on the whole. But to this I can truly answer in the first place that the recoveries were genuine; no patient relapsed, and every one kept well - as I have verified in every case since, in some cases years afterwards, by correspondence with the patients themselves or their relatives. Secondly, I can truly affirm that in every case without exception, the prognosis before treatment was either not good or was actually bad, the patients either remaining stationary as regards their mental condition or becoming obviously worse, notwithstanding a more or less prolonged period of observation under the best auspices of asylum treatment. This fact alone should justify any course of treatment in intractable forms of insanity, even if the rate of recovery were less than 10 per cent, provided always that the treatment be not injurious, as it was not in any of my cases with the exception of perhaps one, that of the senile stout diabetic patient who was one of the earlier cases treated and who, as the experience the profession has since shown, combined in her person three of the contra-indications for the use of thyroid especially in large doses. Thirdly, when it is remembered that my recovery rate is/

is based on all the cases treated; and that I purposely employed thyroid in all the ordinary forms and varieties of insanity acute and chronic, namely in melancholia, mania, stupor, monomania (paranoia), dementia, imbecility, idiocy, recurrent or "periodic" insanity, general paralysis, in alcoholic, morphia, epileptic, phthisical, and post-influenzic cases, and in the insanities of pubescence, adolescence, child-bearing, the climacteric, and senility; when it is remembered that my results are based on this general and indiscriminate use of the drug, it will at once be obvious that a recovery rate of 10 per cent is below the mark as regards the more curable forms of insanity. Eliminating from my 90 cases treated the 2 cases of myxoedema, the 3 congenital cases, the 2 cases of general paralysis, and the 13 essentially chronic cases noted in the preceding table, I find that there remain 65 cases yielding 9 recoveries, that is almost 14 per cent of recoveries. This I would conclude represents the lowest estimate of the therapeutic value of thyroid as a curative agent in the intractable forms of more or less recent insanity. This again is quite apart from its value as an ameliorative agent in both recent and old-standing insanity/

insanity. Did my 9 recoveries (the myxoedemic case being excluded) exhibit any common features which would give an indication as to the kind of case in which thyroid is specially useful in insanity? Did they suggest any one mode of administration as being more effectual than another? Or was there any other fact of practical interest to be derived from a study of the cases?

Eight of the recovered patients were females, and one was a male, but this proves nothing as there were 81 females treated to 9 males. Insane heredity was present in four of the cases. Two of the patients had had previous attacks of insanity. The ages of the various patients were 21, 24, 26, 29, <sup>29,</sup> 30, 38, 43, and 46 years, and were thus most commonly between 20 and 30 years. The clinical types of insanity were as follows:- 1 adolescent, 3 puerperal, 1 lactational, 2 idiopathic (from worry), and 2 climacteric. The mental state of the patients at the time of treatment were:- Secondary (or maniacal) Stupor - 4; Melancholic Stupor, 1; Simple Melancholia, 3; and Delusional Melancholia, 1. The duration of the illness before treatment varied from 4 months to 2½ years, averaging about 9 months for all cases, or, if/

if the  $2\frac{1}{2}$  years' case be excluded, 6 months. The duration of asylum treatment averaged 8 months, or, excluding the  $2\frac{1}{2}$  years' case, 5 months. Large doses of thyroid extract were used in all the recovered cases. I have had no case of recovery from insanity (non-myxoedematous) except with the large doses originally suggested by Bruce and Macphail. This seems to indicate that it is the briskness and intensity of the metabolic reaction which is the essential thing in the thyroid treatment of insanity, rather than a specific tonic effect by the drug on the brain cortex although doubtless this also operates. All the patients reacted well to the drug, the test of the reaction being the loss of weight rather than the pyrexia during the treatment, and more particularly the gain in weight afterwards. The truth of this is borne out by the fact that all the patients lost weight distinctly during treatment, the loss in weight varying from 5 to 10 lbs in the different cases and averaging 7 lbs exactly; and after treatment all gained markedly in weight, the gain in weight averaging over 14 lbs, and in one case actually reaching 46 lbs. Pyrexia however was a more variable index, being "moderately febrile"

(a/

(a rise of  $3^{\circ}$  to  $4^{\circ}$  F) in one case, slightly febrile (a rise of  $2^{\circ}$  to  $3^{\circ}$  F) in one case, distinctly subfebrile (a rise of between  $1^{\circ}$  &  $2^{\circ}$  F) in four cases, poorly subfebrile (a rise of only  $1^{\circ}$  F) in 2 cases, and absent in one case. The only other important feature amongst the recoveries was that at the time of treatment the bodily condition was fair or good, there being no distinct tendency to emaciation, but rather a state of sluggish nutritive equilibrium which required a rousing stimulus. An interesting point I would mention is that out of the 90 patients treated with thyroid, there were in addition to the 10 thyroid recoveries, four other patients who ultimately made good recoveries afterwards, but whose recovery was in no way dependent upon the antecedent thyroid treatment. (See cases 6, 22, 56 and 72). Two of these patients were improved temporarily and two of them were unimproved by the thyroid. This indicates that a patient who does not recover by thyroid treatment may still have a chance of recovery by other means. At the same time my experience is that if a patient is going to recover under thyroid treatment, recovery will occur at the first administration of the drug, and if not then/

then, then not by thyroid. In 30 <sup>cases</sup> patients I have given thyroid twice, or thrice, or four times or even in one case five times, without securing a single recovery.

Thyroid at the same time has its uses in Chronic insanity, as many such cases show more or less temporary improvement after <sup>treatment</sup> ~~the drug~~ - this being indicated by an improved expression of face, more sensible and more responsive conversation, and more settled conduct and better habits. And finally in chronic insanity of a distinctly recurrent type thyroid, given in time and early, will undoubtedly abort an attack of mania, whereas if it be given after the attack has fairly started, it is more likely to aggravate the storm than to calm it.

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P A R A T H Y R O I D   E X T R A C T S .

-oOo-

PARATHYROID EXTRACTS.

The Parathyroid bodies,, which were discovered by Sandström in 1880, are four small flattened reddish-brown bodies, lying adjacent to the lateral lobes of the thyroid gland, one pair ("internal" and "external") being in relation to each lateral lobe. For a long time not much attention was paid to them, the general theory as to their function being that they were embryonic thyroid residues and could take the place of the thyroid in the economy after its removing<sup>al</sup>, either simply enlarging and acting vicariously for it, or actually developing into functional thyroid tissue.

During the past four years however, the experimental<sup>\*1</sup> work more particularly of Vassale and Generali in Italy, of Gley in France, of Blumreich and Jacoby in Germany,<sup>\*2</sup> and of Welsh in this country, has drawn attention to the probable importance of the Parathyroid bodies in the economy. Until recently most of us believed that removal of the thyroid gland is followed by characteristic symptoms although even amongst the thyroidectomists there remain some (e.g. H. Munk) who would attribute the effects produced not to the removal of the gland substance but to an interference with adjacent nerve/

\*<sup>1</sup>Italian Retrospect). Scott. Med. & Surg. Jo. ~~Apr. 1897~~  
~~& Journ. Med. Sc. July 1897 & July 1898~~ Journ. Med.

\*<sup>2</sup>Welsh. Journ. Anat. & Phys. Jan. & Apr. 1898. 1898.  
 and Journ. Pathol. & Bacter (~~&c.~~ July 1897

nerve structures in the neck involved by the operation. More recently however, the parathyroidectomists have appeared on the field and although they are still a divided camp, some of them (e.g. Blumreich & Jacoby) holding that one and all of the parathyroids may be removed without ill effects, the majority of them maintain that their experiments favour the view that the time-honoured acute effects of thyroidectomy are to be attributed to the removal of the parathyroids alone. The experimental removal of the thyroid ~~and para-~~<sup>has</sup> ~~para-~~thyroids thus led to very conflicting views and would seem to raise the possible question that the parathyroids were physiologically more important than the thyroid, and that possibly the activities of thyroid preparations might be due to an admixture of parathyroid. \*

It therefore occurred to me that light might be thrown upon the matter from the pharmacological side by the administration of parathyroid extracts, which had not previously been exhibited in the human subject. One would thus be able to compare the effects produced with those which occur during thyroid administration.

Diseases of the parathyroids may occur, but they appear to give rise to no <sup>constitutional</sup> symptoms, and tumours (as in the case reported by ~~Smith\*~~<sup>Santi\*</sup>) seem to produce no effects/

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\* "The action of thyroid and parathyroid extracts upon metabolism in the insane." Lancet 28. August 1898.

X Santi. Med. Press & Circ. 6<sup>th</sup> Sept. 1899.

effects apart from local pressure complications. According to Vassale however, the symptoms of "parathyroid insufficiency" which follow parathyroidectomy are the same as the acute nervous and tetanic phenomena which sometimes follow thyroidectomy in animals. "Curiously the symptoms of parathyroid insufficiency are entirely relieved by exhibition of large doses of thyroid, a fact which strongly suggests to me that they are really attributable to a damaged thyroid. In one of Vassale's experiments on a bitch, all the parathyroids except one (left internal) and the thyroid were removed. All went well till she gave birth to a litter of pups and began to suckle them, when acute "tetania" supervened but was relieved and kept in check by thyroid administration until lactation was over safely, after which the animal remained well. This experiment again suggests to me that the symptoms were really those of thyroid insufficiency taking the acute neurotic form seen in young animals, the thyroid insufficiency possibly being due to a severe call upon the (previously damaged) thyroid by the actively metabolic mammae of commencing lactation. May there not similarly be an element of thyroid insufficiency in the production of the acute puerperal and lactational insanities, which amongst my cases of thyroid treatment gave by far the best results. An actively metabolic organ, such as the pregnant or puerperal uterus or/

or the mammae of lactation, will probably make an extra demand on the thyroid, and unless the latter respond sufficiently, other organs, as the brain cortex, will suffer. This may possibly <sup>partly</sup> explain some of the special value of thyroid extract in puerperal and lactational cases.

#### ADMINISTRATION OF PARATHYROID EXTRACT.

The Parathyroids of the ox were selected, this being the most convenient animal from which to obtain a sufficient supply of these small bodies. Welsh,\* who has recently given an excellent account of the anatomy of the parathyroids in man and of the effects of their removal in cats, was kind enough in the first instance to make me familiar with their appearance in the ox. In order to avoid any risk of removing thyroid tissue along with the parathyroids, I employed only the external parathyroids, these being anatomically separate from the thyroid, and not, like the internal bodies, incorporated with the larger gland. The external parathyroids of the ox lie, one on each side, just under cover of the free dorsal borders of the lateral lobes of the thyroid, opposite about the lower level of the isthmus. They occupy the stratum of fat which separates the thyroid lobe ventrally from the/

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\* op. cit.

the pharynx-oesophagus dorsally. Not infrequently they are blended with islets of thymus tissue. They are usually somewhat flattened and pyriform, the sharp end directed towards the middle line, being continuous with a stalk or pedicle which contains the blood vessels and penetrates the deep surface of the thyroid. They measure from  $\frac{1}{4}$  to  $\frac{1}{2}$  an inch in length and weigh from a half to one grain. *(The thyroid of the ox weighs full 1 oz)* They have a smooth surface and a reddish brown colour, and their cut surface is relatively dry and lacks the juicy appearance of fresh-cut thyroid tissue. Microscopically they consist of closely packed groups or columns of cubical epithelial cells, with a delicate interwoven stroma and in places there is an appearance of a lumen in which there is sometimes colloid like material. The parathyroids of the ox, like these in man, may thus exhibit what Welsh describes as the more highly specialised types of structure. The chemistry of the parathyroids is unknown.

Parathyroid extracts were administered in three cases with the following results:-

#### CASE I-

(E.T.) 38. Female. At 25 had tubercular disease of lumbar vertebrae which became quiescent but left her kyphotic and paraplegic. At 35 "Phthisical" mania, delusional, irritable, suspicious, gradually became chronic/



chronic; in asylum for three years at time of treatment. In this my first case of parathyroid treatment I commenced the drug on the 5th day of rest in bed with fixed diet. In the first instance the fresh glands were dried for 24 hours in a Sulphuric acid chamber and administered by the mouth. In this way one dried gland was given by the mouth every morning for a week (5th to 11th days), two dried glands were given on the 12 and 13th days, and three on the 14th day. No effects were observable. On the 15th and again on the 16th day three glands <sup>diss</sup> ~~dese~~cted the same morning, were administered straight away in the fresh state by the mouth, but without any apparent change in temperature, pulse, respirations, urine or in metabolism generally. As mouth administrations gave negative results, hypodermic injections were tried after an interval of 5 days (17th to 21st). <sup>Extracts</sup> ~~Extraxts~~ in glycerine were used, and in this form one gland was given on the 22nd. day, 2 were given on the 23rd and 24th days, and three on the 25th day. During the treatment by subcutaneous injections of glycerine extracts the patient was kept under careful observation, the temperature being taken every hour day and night. The only changes noticed were (1) a slight diminution in the red blood corpuscles: this quite probably was due to the interference with the patient's sleep,

sleep involved by the taking of the temperature.  
 (2) a slight increase in the <sup>di</sup>precrotic wave of the pulse-curve. A rise in pulse-tension however has been frequently observed to follow the subcutaneous injection of certain other animal extracts, so that one was not justified in inferring that this was a specific action of parathyroid extract.

No therapeutic effects followed, and the patient is still insane and in the asylum.

#### CASE II-

(S.H.) 38. Female. Mother insane. Patient was a prostitute and has syphilitic cicatrices. At 36 general paralysis: ill three years. In this the second case extracts were made in glycerine, in sulphuric ether, and in 10% sodium chloride solution. They were injected subcutaneously, the doses in the case of each extract being equivalent to from 1 to 4 fresh glands. The results were again negative, though the treatment was persisted in for seven weeks. In This case the glycerine extracts produced no diminution of red blood corpuscles, the ethereal extracts produced a transient quickening of the pulse apparently due to the ether, and the saline extracts produced no effect at all. She was unimproved therapeutically and died six months later of her disease.

#### CASE III-

(Mrs. C.L.A.H.) 50. Female. At 45 <sup>clin</sup>Chin~~acteric~~  
Melancholia, with suspicious and hypochondriacal ideas:

ill 5 years. In this third case glycerine extracts were given hypodermically containing in each daily dose as much as 9 fresh glands, that is more parathyroid than would be found associated with two thyroid glands in the whole animal. No change occurred in temperature, pulse or respirations, no increase in the output of water and carbonic acid, no change in the urinary nitrogen and phosphoric acid, (which was estimated daily), and in short the patient exhibited none of the constitutional effects of thyroid feeding on the contrary she actually gained 2 lbs in weight during the treatment. After a few days' interval she received thyroid treatment by the stomach in doses equivalent to one fresh thyroid daily, and she at once exhibited the effects of the drug in a marked degree, and lost 10lbs in a week. This case proves conclusively that in a patient actively susceptible to thyroid, parathyroid even in relatively larger doses produces no effects comparable to those which occur during thyroid administration. And indeed in my hands the external parathyroids of the ox when administered to the human subject, whether in the solid state (dry or fresh) by the mouth, or in the form of glycerine, ethereal, or saline injections under the skin, seem to produce no effect at all except a slight increase in pulse-tension in common with but to a less extent than certain other organic extracts. No therapeutic results were obtained in any of the three cases treated with/

with parathyroid extracts, ~~at all~~.

Parathyroid extract therefore is probably inert pharmacologically and therapeutically useless - and so differs entirely from thyroid extract.

The symptoms of parathyroidectomy and the acute neurotic symptoms of thyroidectomy are one and the same, and in my opinion proceed from the thyroid factors alone, and may be explained by:-

(1)

The youth of the animal operated upon: the "acute" symptoms are always most common in young animals, probably because the thyroid is more essential to nutrition in the young.

(2)

The interference with the rich nervous connections of the thyroid during the operation.

(3) The wounding of the thyroid, in consequence of which colloid is spilt and thyroidism is produced by the rapid absorption of the juice by the raw wound surfaces. Where surgeons meet with this mishap it is common for them to have a more than usually distinct febrile reaction and tetanic symptoms after the operation. In fatal cases of thyroidectomy death occurs usually <sup>by</sup> in rapid heart failure, and as we have seen the toxic effects of thyroid extracts are most marked upon the circulation. In the removal of the internal parathyroids which are usually incorporated in the deep surface of the thyroid, the thyroid cannot escape severe manipulation or even actual wounding.

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From:-

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Organo-Therapeutics in the Insane (contd.)

by C. F. Asst. Enbrook, M.A., M.B.

Cerebral Extract. p. 1.

Ovarian Extract. p. 10.



## Cerebral Extract.

The Brain not being a glandular organ in structure or function, would a priori hardly be thought to possess an "internal secretion" in the ordinary sense of the term. Its essential nerve elements arise from the neural Epiblast, its vessels and accompanying connective tissue from the mesoblast, and the neuroglia according to Fard Robertson probably arises from both Epiblast and mesoblast. Adult Brain tissue consists roughly in the fresh state of 78% water and 22% solids, the water being relatively more abundant in ~~the~~ <sup>than in adult</sup> early life, and in the grey than in the white matter. The solids (~~the~~ <sup>eg. as in</sup> dry brain extracts) consist mainly of proteins (especially a nucleo-proteid), phosphorised fatty constituents (eg. protagon and Lecithin), and cholesterol (~~a~~ <sup>an</sup> alcohol which forms with fatty acids the fatty compounds called "esters"). The proteids and phosphorised constituents are most abundant in the grey matter (whose solids consist of 51% proteins alone). Cholesterol is most abundant in the white matter, forming 51% of its solids.

The brain solids also comprise neurokeratin (in the neuroglia especially), nuclein, cerebroside, & other obscure intraglanous bodies, and small quantities of extractives and inorganic salts.

Brain Extracts were first administered in disease by Brown-Séquard and his followers, who claim that Cerebral or Medullary Fluid,

(a glycerine extract of the grey or white matter of the brain), injected subcutaneously, is beneficial in neurasthenia, locomotor ataxia, chorea (Montagnon), and especially in epilepsy (Babes and Gillies).

Althaus claims that his Cerebrine Alpha and Myeline Alpha — glycerine extracts of brain and spinal cord respectively — are nerve tonics, useful especially in functional nervous affections but also in organic diseases of the <sup>central</sup> nervous system.

In mental diseases Brain Extracts have been administered, but with indefinite results, by A. Robertson in 17 cases, by Ryan in 6 cases, and in a few unpublished cases by Macphail, Bruce, and others. Ryan employed hypodermic administration of glycerine extracts but his cases show nothing definite. Robertson employed <sup>the</sup> glycerine extract ("Myelin") and the

\* Brit. Med. Journ. 1893. I. p. 1213.

\* Lancet. 1893. II. 1376.

\* B.M.J. 1894. I. 240.

\* B.M.J. 1893. II. 1319, + 1896. II. 800. \* B.M.J. 1896. II. 801.

dry Extract ("Cerebrine" Tablets) of sheep's  
brain, given in both cases in the mouth.

Robertson found no characteristic physiological  
or therapeutic effects in his cases, but he  
is inclined to think that <sup>Brain Extract</sup> it may act as a tonic  
in mild and early cases of neurasthenia and  
insanity.

Hammond of New York stated that hypodermic  
injections of his preparation "Cerebrine"  
produced various remarkable physiological  
effects in himself. But <sup>X</sup>Stockwell of Detroit,  
procuring some of ~~Hammond's~~ <sup>the</sup> "Cerebrine"  
from Hammond himself found it absolutely  
inert in several healthy workmen!

The following is a Summary of my own  
experience of Cerebral Extract in 16  
cases of insanity. The patients were women,  
varying in age from 20 to 55, and suffering from  
mental disease which was either chronic  
or threatening to become so. They were in most cases  
treated in bed and on a fixed mixed diet  
to ensure more accurate observations, but  
Brain Extract can be given freely to and  
without risk to patients going about in the  
pursuance of their ordinary affairs.  
X. Lancet. 1893. II. 753.

The form of Brain Extract employed in all cases was the Tablet preparation ("Cerebrin") or dry extract of sheep's brain, and it was administered by the stomach. The doses per diem varied from 15 grs. to 90 grs. <sup>(ie 3 to 18 tablets)</sup> and were continued for 2 to 3 weeks. Most patients got on an average 60 grains a day for 3 weeks, that is in all about 1200 grains. The smallest quantity given was 720 grains in 14 days; the largest amount was 1890 grains in 21 days.

## I. Pharmacology.

1. Temperature in 8 cases was unaffected; in the other 8 there was a more or less continuous subfebrile pyrexia which was poor (a rise of  $1^{\circ}7$ ) in 4 cases, and distinct (a rise of between  $1^{\circ}$  &  $2^{\circ}7$ ) in the other 4 cases.
2. Weight was unaffected in all ~~cases~~ <sup>cases</sup> except ~~3~~ <sup>3</sup> in which there was a loss of 2, 4, & 5 lbs. respectively.
3. Integumentary Locomotory & Muscular Systems <sup>increased</sup> unaffected, perspiration being the only thing noted in only one case.
4. Nervous Sys. In 3 cases the patients became more excitable talkative and impulsive during treatment.

noticed. The

5. Circulatory S. No change; pulse ~~was~~ <sup>was</sup> quite unaltered in frequency or otherwise. In a semi-control experiment on myself, a dose of 30 grs. (6 tablets) produced for half an hour afterwards a distinct increase in the height of the "a" deflection and in the "diastolic wave" of the sphygmogram.

6. Respiratory S. In 1 case <sup>the</sup> respirations were increased by 4 (on an average) during treatment.

7. Alimentary S. Nausea & Vomiting in 2 cases. Diarrhoea in one.

8. Urine - Gen. & Spec. S. The urine showed no ~~marked~~ change except a slight increase in the total solids <sup>increase</sup> (averaging 66 grains daily) and in the urea (averaging 33 grains daily).

Menstruation occurred in 1 case at the onset of treatment (this being the regular period), and again irregularly during the second week. In another case (puerperal) menstruation which had been in abeyance for 18 months reappeared on the 7<sup>th</sup> day after cessation of the extract.

Conclusions. <sup>Dry</sup> Brain Extract produces a slight increase in protein metabolism, probably due to its large percentage of nitrogenous matter. This may also explain the only other common feature - the pyrexia. The other changes are probably accidental and not characteristic.



II. Therapeutics. The 16 patients, all female, gave the following results:-

- 1 (J.N.). Aet. 20. At 19 Adolescent Melancholic Stuper, continues, is unimproved by thyroid at 4<sup>th</sup> month of illness; worse after influenza at 7<sup>th</sup> month, <sup>improved, and finally two months later</sup> becomes maniacal (simple mania) after ovarian extract at 10<sup>th</sup> month, and remains maniacal till cerebral extract treatment at 18<sup>th</sup> month: therefore ill 18 months (in a syrium): has 900 grs. of Brain Extract in 15 days, with good Subile pyrexia; during the next 2 weeks after Brain Extract the mania, which had lasted 8 months, began to subside, and the patient steadily became well and recovered after a 20 months' illness. Whether the subsidence of the mania (simple excitation in type) was due to Brain Extract or not, I am unable to say.
- 2 (M.S.). 25. At 24 Adolescent Mania (simple), with incipient Dementia: ill 1 $\frac{3}{4}$  yrs. Improved temporarily.
- 3 (E.M.). 29. At 27 Adolescent Melancholic Stuper, with Secondary dementia: ill 2 $\frac{1}{2}$  yrs. Unimproved - on last day of Extract had a very short but violent attack of impulsive Excit Emot.
- 4 (H.B.S.P.). 32. At 25 Adolescent Mania (severe), then Dementia: ill 7 yrs. Unimproved.

- 5 (W<sup>rs</sup> M.N.H.). 31. At 30 Puerperal Mania (severe), then stuporose and delusional: improved by thyroid at 4<sup>th</sup> month, but remains suspicious & taciturn & stuporose: ill 8 months (7 in a syphilis): given Brain Extract (945 grains in 14 days): no change in temperature, weight, pulse, or respiration, but urinary solids sub increased. On 7<sup>th</sup> day after treatment, menstruation reappeared for first time & recovery set in and was complete. Whether Brain Extract initiated <sup>the return of</sup> menstruation and recovery is uncertain.
- 6 (W<sup>rs</sup> H.F.D.) 30. At 29 Lactational Melancholia (suicidal), passed into mania (moderate) with incipient dementia: ill 2 yrs: unimproved.
- 7 (W<sup>rs</sup> H.F.W.) 38. At 37 Post-Febile Mania (after typhoid), passed into stupor with incipient dementia: lungs tubercular: ill 10 mos. Unimproved.
- 8 (H.M.). 28. At 24 Post-Febile Melancholic Stupor (after influenza), then cataplexy and dementia: ill 3 1/2 yrs. Unimproved.
- 9 (W<sup>rs</sup> H.C.M.). 37. At 36 Syphilitic Mania (moderate), becoming chronic: rupia present. Potassium iodide relieves rupia but not mania: ill 1 3/4 yrs. Unimproved.
- 10 (J.P.). 34. Prostitute. At 34 Alcoholic Mania (delusional), becoming chronic: ill 1 1/2 yrs. Unimproved.



- 11 (W<sup>rs</sup> M. S. D.). 48. At 48 General Paralysis (delusional & excited type): ill 11 mos. Unimproved.
- 12 (W<sup>rs</sup> J. R. M.) 38. At 38 Idiopathic Mania (from adversity), delusional & excited, vivid hallucinations of hearing: ill 9 mos. Unimproved.
- 13 (W<sup>rs</sup> B. C. D.). 34. At 31 Idiopathic Mania (from grief at deaths of favorite son & sister) & becoming demented: lungs tubercular: ill 3 yrs. Unimproved.
- 14 (R. E. W.). 47. At 46 Climacteric Mania (delusional), becoming chronic: ill  $1\frac{3}{4}$  yrs. Unimproved.
- 15 (W<sup>rs</sup> F. B. L.). 45. At 43 Climacteric Melancholia, becomes delusional & manic: ill 2 yrs: improved.
- 16 (W<sup>rs</sup> M. W. A.). 55. At 54 Senile Melancholia, <sup>and rheumatic</sup> prematurely old and feeble: becomes after ovarian treatment severely manic, and remains a Senile chronic manic: ill  $1\frac{1}{2}$  yrs: improved.

~~Since~~ Hence 2 cases recovered, 3 were improved, and 11 were unimproved after cerebral extract treatment. The recoveries may or may not have been "propter hoc", but they were very definitely "post hoc".

Those improved looked brighter and smarter, talked more sensibly, ~~and~~ were more approachable and more easy to do with, and better in many of their habits: this may have partly been due to the extra nursing and attention during treatment.

My cases indicate that for future  
trial of Brain Extract <sup>in mental diseases,</sup> Simple mania,  
~~and~~ mild secondary & stupor, and insanity  
accompanied by <sup>temporary</sup> functional aneurvthema  
<sup>the forms</sup> are most likely to be benefited.

Ovarian Extract.

Ovarian Extract.

The Essential Elements of the ovary, the  
ovisacs and ova, are derived from a specially  
modified or "germinal" portion of the epithelial  
lining of the embryonic body - cavity, this  
again being formed by the previous splitting  
of the moriblast into two layers. Probably  
all the permanent ova are formed before  
birth, many of them <sup>never</sup> ~~lead~~ to maturity at  
all — the number in each ovary being  
reckoned at tens of thousands, and there-  
fore probably exceeding safely the require-  
ments of the organism — and all  
close to mature after the menopause;  
and in old age the ovaries atrophy. The solids  
<sup>(Eggs in dry Extracts)</sup>  
of the ovary ~~are composed~~ consist almost  
entirely of protein or allied substances,  
the ova and ovisacs being composed chiefly  
of nuclein and nucleo-protein but also of  
the simpler proteins, cell-globulin and cell-  
albumin; and the stroma yielding  
According to Bach the ovary like the  
testis contains spermin.  
mainly nuclein and gelatin. Removal of  
the ovaries profoundly modifies general  
nutrition and the development of other organs,  
and while Brown-Séquard would attribute  
B.M.J. 1893 I. p. 1213

these effects to absence of an "internal secretion", Schaffer<sup>x</sup> and others would explain them as the result of a reaction upon the rest of the body through the nervous system. Brown-Séquard states that "ovarian fluid" (a glycerine extract of ovarian tissue), injected subcutaneously, acts as a tonic to the nervous and muscular systems, and given to old women greatly improves their physical nervous and mental energies, acting similarly to orchitic fluid but not so powerfully. Schaffer suggests that these effects may simply be due to a richness of nuclein in the extract. Intravenous injection of aqueous ovarian extract produces similar effects upon blood-pressure to <sup>those of</sup> the majority of organic extracts, namely a slight temporary fall. } A single large dose of dry extract taken in the stomach produced no visible effect in my own case upon ~~the~~ pulse tracings until 25 minutes afterwards, when the ascent of the ~~was~~ curve was distinctly increased. } Ovarian extracts have been found most beneficial in failing senility, and in the  
x Physiol. op. cit. p. 937.

various disorders (sympathetic nervous,  
e.g. flushings, perspirations, palpitation,  
headaches, insomnia) of the climacteric,  
whether this occur at the ordinary time  
or prematurely or artificially from  
oöphorectomy. It has also been given  
beneficially in amenorrhoea and other  
functional disorders of the female reproductive  
system; also in chlorosis; also in  
thyroid insufficiency and exophthalmic  
goitre, and in epilepsy and hystero-epilepsy.  
Ovarian Extract has not been much  
employed in mental diseases, and  
Buschan in his recent work on Organo-  
therapy (Berlin, 1898) mentions only 7  
cases, ~~of whom~~ <sup>the one</sup> 5 ~~were~~ women and 2 ~~were~~  
men - 3 women with melancholic stupor  
being cured, 1 hystero-epileptic woman  
being improved, and the remaining female,  
a castrated hypochondriac, being made worse;  
while of the two men, <sup>the one</sup> a <sup>maniac</sup> was  
improved, and <sup>the other</sup> a hystero-epileptic, ~~was~~  
became worse. Three cures out of 7  
cases is a striking result, and accordingly  
I have tried ovarian Extract somewhat  
extensively amongst my present patients.

I have administered dry ovarian Extract in Tablet form in 36 cases, in the Stomach in every instance. The doses given per diem varied from 15, to 30, to 45, to 60, to 90 grains in the various patients, the treatment being continued for usually 2 or 3 weeks but in the various cases from 1 week to 10 weeks. The smallest quantity given was 300 grains in 5 days: the largest was 3450 grains in 10 weeks: most patients had within 2 or 3 weeks from 600 to 1200 grains.

### Pharmacology

- 1 Temperature, in about a third of the cases was raised continuously  $\frac{1}{2}$  to  $1^{\circ}F$ : in most cases unaffected, and in a few lowered  $\frac{1}{2}^{\circ}F$ .
- 2 Weight, mostly unaffected: sometimes 2 or 3 lbs <sup>more</sup> above, sometimes 4 or 5 lbs less.
- 3 Integumentary & Locomotory Systems, unaffected.
- 4 Hæmopoietic S. mostly unaffected.

Red blood corpuscles & Haemoglobin sometimes a little increased; sometimes slightly diminished, in one case markedly so.

- 5 Nervous S. Paros in the limbs and head



occurred in 5 cases; and in about a third there was temporary increase of mental excitability. An increase of vigour & strength did occur distinctly in two prematurely senile cases.

6 Circulatory S. Pulse frequency unaffected usually but sometimes diminished distinctly. pulse-tension in most of the tracings showed a slight increase.

7 Respiratory S. Respiration in a few cases were diminished but mostly were unaffected.

8 Alimentary S. Nausea and biliousness in 3 cases.

9 Utero-generative S. Menstruation was occasionally more profuse than usual at the regular periods, but in only 5 cases did it occur irregularly. The urine showed a slight increase in total solids and urea but otherwise was unaffected.

Pharmacologically therefore dry ovarian Extract produces no characteristic phenomena apart from occasional pyrexia, slight azoturia and increased menstruation all of which effects could probably be produced by any other protied Extract.

## II Therapeutics.

The patients, all females, were either chronically insane or becoming so, and ~~the cases included~~:-

- 1 Congenital imbecile (21), 1 Pubescent Epileptic with <sup>mild</sup> mania (14 years), 1 Pubescent incipient dement (17), 1 Adolescent stuporose melancholia (20), 1 Adolescent Cataleptic and incipient dement (24), 2 Adolescent incipient dement (both aet. 24), 1 Adolescent confirmed dement (32);
- 1 Post-concussional stuporose melancholic (25), 1 Lactational maniac becoming demented (30), 1 Post-influenzic incipient dement (27), 1 Post-typhoid stuporose and incipient dement (37), 1 Alcoholic maniac (38: ~~had~~ had a simple cyst of left broad ligament removed 7 years previously); 1 Alcoholic morphinomaniac (39), 1 General Paralytic (46); 4 Idiopathic cases viz 1 Simple Melancholia (55: had a scirrhus mamma removed at 54), 1 Delusional melancholia (36), 1 Delusional maniac (34), and 1 incipient dement (34); 11 Characteric cases, viz 2 Simple Melancholias (49, 51), 3 Delusional Melancholias (41, 46, 46), 2 Excited Melancholias (41 & 46), and 6 Delusional maniacs (44<sup>(2)</sup>, 45, 46<sup>(47)</sup>, 48).
- 3 Severe Melancholias - Simple (55<sup>(2)</sup>, 65), and Excited (63); and finally two cases of ovarian insanity - 1 a stuporose melancholia (56); and 1 a chronic maniac (33).

Two of these patients recovered :-  
One of them, an Idiopathic Melancholic of 55  
who had worried over the removal of  
her Breast (carcinomatous), recovered  
long after <sup>the</sup> ovarian extract treatment,  
which therefore had no influence in  
the recovery. The other, an adolescent  
Stuporose Melancholic of 20, brightened  
up at the end of treatment, menstruated  
for the first time for 8 months a fortnight  
after the drug, and at the 3<sup>rd</sup> menstruation  
(2 months later) passed into a state of  
Simple Mania which lasted 8 months  
and subsided (immediately after  
Brain Extract treatment) and made  
a good recovery - probably partially  
brought about by ovarian administration.  
All the other ~~two~~ patients were  
unimproved by ovarian extract, but  
all were not unaffected by it. The  
two ovarian cases were (1) A Stuporose  
Melancholic who had had cystic  
disease of the ovaries for 9 years, but  
had become <sup>recently</sup> insane from financial  
worries: ~~only~~ she was given 1320  
grains in a month, showed no change  
at all, died 9 months later, and at

the post-mortem Examination the  
cyst of the left ovary (which filled most  
of the abdominal cavity) weighed  $9\frac{1}{4}$  lbs,  
and the cyst of the right ovary (which  
occupied the pelvic cavity) weighed 14 oz.  
The other "ovarian" case ~~had~~ had had  
much ovarian trouble with erotic tendencies  
in her adolescence; at 31 double oophorectomy  
was performed and she became maniacal  
& remained so; at 33 she had ovarian  
extract in large & long continued doses  
but she still remained, as she is now,  
a chronic maniac.

Two if not three of the patients  
however did show some distinct mental  
effects after treatment. (1) One, a characteristic  
excited melancholic of 46, of prematurely  
senile appearance, became distinctly more  
vigorous and stronger and consequently  
still more excited mentally. (2) Another,  
a senile melancholic of 55, of markedly  
senile appearance for her years, and  
in a very enfeebled and exhausted  
ratty condition, had 1350 grams in 40  
days, and became so vigorous that

She "veritably" took up her bed and walked, and instead of being unable to leave her bed owing to weakness she was able to stand it up on its end and to defy the nurses to interfere with her. She passed <sup>from melancholia</sup> into a severe attack of mania which was very violent for 3 months and now, 4 years later, still remains in a chronic form. And (3) the remaining patient was the pubescent epileptic girl of 14, who after taking 800 grains in 9 days became acutely and severely maniacal for 3 days, with loud screaming, mental confusion, and rigid flexion of all her limbs. This however passed off and left her as before.

As to the results with mammary, uterine, and ovarian extracts; and with the splenic and suprarenal extracts, — no striking therapeutic or pharmacological features occurred in my cases.

CC Eastbrook